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DISEASES OF THE DIGESTIVE SYSTEM

EDITED BY

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Third Edition, Thoroughly Revised

With 269 Engravings and 5 Color Plates



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AFFECTIONATELY DEDICATED TO MY BROTHER

DR MILTON M PORTIS

MY FIRST TEACHER IN GASTROENTEROLOGY

PREFACE TO THE THIRD EDITION

The enormity of the problems of gastroenterologic disturbances and the high incidence of gastrointestinal ailments among patients coming to the attention of general practitioners and the various specialists necessitate frequent re-evaluation of the scope of and advances in the field of gastroenterology. The short space of time—six years—since the second edition has brought forth new knowledge in the handling of gastrointestinal dysfunction. A large number of the psychosomatic problems manifested among members of the Armed Forces during World War II and after their return to civilian life are related to the gastrointestinal tract. Both gastroenterologists and psychiatrists have had an opportunity to study these patients from a combined or single approach. One of the major objectives in previous editions—to a greater extent in the second edition—was to elucidate some of these problems; the third edition will attempt to clarify them further.

The psychodynamics and the psychogenesis of this pathological physiology, presenting bizarre clinical pictures which are so often erroneously classified under "nervous indigestion" and a host of similar inadequate diagnoses, are most ably considered in such chapters as those by Franz Alexander, Stewart Wolf and Thomas P. Almy. In addition, the other contributors have taken into account the psychogenic factors of the various problems discussed in their chapters and have approached the evaluation of them with sound clinical judgment. Practically every chapter has been extensively revised, and many new authors have been added. They include M. I. Grossman, J. P. Quigley, Stewart Wolf, Stanley Cobb, Avery Weisman, Albert Milzer, William Sawitz, Bernard Sarnat, Edward Berk, Mitchell Spellberg, Leon Schiff, Robert Elman, William R. Hewitt, William H. Daniel, Robert Greenblatt, Leo Rigler and A. Stephens Graham. The chapters have been rearranged especially to facilitate the teaching in gastroenterology. The physiology of the gastrointestinal tract is discussed in its entirety as groundwork for a thorough understanding of the clinical manifestations.

The very enthusiastic reception accorded previous editions by students, teachers and practitioners has been most gratifying and has stimulated me in the preparation of this new edition. It has been my desire to present the field of gastroenterology in its most modern and scientific aspects. To all contributors who have made this book possible I am deeply grateful.

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CONTENTS

CHAPTER 1

CHAPTER 7

THE PHYSIOLOGY OF THE SMALL AND THE LARGE INTESTINE

By J P QUIGLEY Ph D

CHAPTER 8

PHYSIOLOGY OF THE MUCOUS MEMBRANES AND DIRECT OBSERVATIONS ON GASTRIC AND COLONIC FUNCTION IN MAN

By STEWART WOLF M D

CHAPTER 9

NEUROLOGICAL ASPECTS OF GASTROINTESTINAL DISEASE

By AVERY D WEISMAN M D and STANLEY COBB M D

CHAPTER 10

By CHESTER M JONES M D

CHAPTER 11

EMOTIONAL FACTORS IN GASTROINTESTINAL DISTURBANCES

By FRANZ ALEXANDER M D

CHAPTER 12

HYPERINSULINISM AND FATIGUE

By SIDNEY A. PORTIS, M.D.

CHAPTER 13

ALLERGY OF THE GASTROINTESTINAL TRACT

By GEORGE PINESS, M.D.

CHAPTER 14

ANEMIAS OF GASTROINTESTINAL ORIGIN

By RAPHAEL ISAACS, M.A., M.D.

CHAPTER 15

DIETETIC CONCEPTS OF GASTROINTESTINAL DISEASE

By KATE DAUM, PH.D.

CHAPTER 16

THE ROLE OF ROENTGENOLOGY IN THE DIAGNOSIS OF DISEASES OF THE DIGESTIVE TRACT

By LEO D. RIGLER, M.D.

CHAPTER 17

THE TONGUE IN HEALTH AND DISEASE

By BERNARD G SARNAT M D

CHAPTER 18

RELATION OF THE TEETH TO GASTROINTESTINAL DISEASES

BY E H HATTON M D

CHAPTER 19

DISEASES OF THE ESOPHAGUS

By PORTER P VINSON, M D

CHAPTER 20

CLINICAL ASPECTS OF GASTRIC SECRETIONS

By ARTHUR L BLOOMFIELD M D

CHAPTER 21

GASTRITIS

By RUDOLPH SCHINDLER M D

CHAPTER 22
Peptic Ulcer
By Walter Lincoln Palmer, M.D.

CHAPTER 23
Indications for the Surgical Treatment of Peptic Ulcer
By Warren H. Cole, M.D.

CHAPTER 24
Cancer of the Stomach

CHAPTER 25
Linitis Plastica

CHAPTER 26
Benign Tumors

CHAPTER 27
Syphilis of the Stomach

CHAPTER 28
Diseases of the Extrahepatic Biliary Passages
By Sidney A. Portis, M.D. and S. Philip Bralow, M.D.

CHAPTER 29

Treatment of Diseases of the Gallbladder and Extrahepatic Bile Ducts

By J Edward Berk M D Sc D

CHAPTER 30

Diseases of the Liver

By Sidney A Portis M D

CHAPTER 31

VIRAL HEPATITIS

CHAPTER 32

NEEDLE BIOPSY OF THE LIVER

CHAPTER 33

DISEASES OF THE PANCREAS

By ROBERT ELMAN, M D

CHAPTER 34

DISEASES OF THE SMALL INTESTINE

By FRANZ J INGELFINGER M D

CHAPTER 35

REGIONAL ILEITIS

CHAPTER 36

The Problem of the Vermiform Appendix

By Owen H. Wangensteen, M.D.

CHAPTER 37

Functional Disturbances of the Colon

By Thomas P. Almy, M.D.

CHAPTER 38

Nonspecific or Indeterminate Ulcerative Colitis

CHAPTER 39

Bacillary Dysentery

By Joseph Felsen, M.D.

CHAPTER 40

Protozoan Infections of the Intestine

By William G Sawitz M D

CHAPTER 41

The Metazoan Parasites of the Gastrointestinal Tract

By Ernest C Faust M A Ph D

CHAPTER 42

Intestinal Tuberculosis

By W R Hewitt M D

CHAPTER 43

EFFECT OF SULFONAMIDES AND ANTIBIOTICS ON THE INTESTINAL FLORA

By ALBERT MILZER M D

CHAPTER 44

DIVERTICULOSIS AND DIVERTICULITIS

CHAPTER 45

CANCER OF THE COLON

CHAPTER 46

CANCER OF THE RECTUM

CHAPTER 47

OTHER DISEASES OF THE RECTUM

By WILLIAM H DANIEL M D and GEORGE C TYLER M D

CHAPTER 48

GASTROINTESTINAL MANIFESTATIONS OF ARTHRITIS GOUT AND DIABETES

By FRANKLIN R NUZUM M D

CHAPTER 49

GASTROINTESTINAL MANIFESTATIONS OF ENDOCRINE DISORDERS

By ROBERT B GREENBLATT M D and WILLIAM E BARFIELD M D

20 TUCHMANN H Modifications de la structure Histologique de l Hypohyse du Cobage Normal et Castré à la suite d Injections Hormonales Compt rend Soc Biol 125 635 1937
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Chapter 2

THE PHYSIOLOGIC FUNCTIONS OF THE HYPOPHYSIS

The Hormones Elaborated by the Pituitary Body

The Hormones of the Pituitary Gland —Hormones are elaborated both by the adenohypophysis and by the posterior lobe of the pituitary gland The pars distalis probably represents the active secretory portion of the adenohypophysis, while the processus infundibularis is the only established secretory component of the posterior lobe The hormone fractions to date identified with activity of the adenohypophysis include

1 Growth hormone
2 Gonadotropic hormones
3 Thyrotropic hormone
4 Adrenocorticotropic hormone
5 and possibly a Diabetogenic hormone

The posterior lobe secretes a

1 Vasopressor principle
2 Antidiuretic factor
3 Oxytocic factor

Hormones of the Adenohypophysis —There has been considerable discussion as to the exact number of hormones elaborated by the adenohypophysis The existence of many different fractions has been postulated but only those mentioned above have been generally accepted Such fractions as the parathyrotropic factor the medullotropic and pancreatropic factors the ketogenic glycogenic glycostatic melanophore-expanding and contra insulin principles have been described Studies dealing with these fractions have been so meager and contradictory however that their existence as individual specific hormones is questionable

There has been a good deal of difference of opinion as to whether the acceptable hormones of the adenohypophysis constitute actual individual hormones or whether they simply represent prosthetic groups of one or more large basic protein hormones Thus Collip[1] has suggested that only three hormones are elaborated by the pars distalis These are

1 A protein molecule concerned with growth promotion lactation adrenal cortical function carbohydrate and fat metabolism,

2 Another protein molecule concerned with thyroid function the formation of the corpus luteum and the stimulation of the cells of Leydig of the male which results in the production of the male sex hormone and

3 A final protein hormone which elaborates estrogen in the female and induces spermatogenesis in the male

Riddle[2] has advanced considerable evidence to indicate that various adenohypophyseal fractions play a role in body growth These data

would theoretically therefore cast some doubt on the separateness and singleness of a growth factor elaborated by the pituitary gland

The ultimate proof of the existence of these various fractions as separate and individual hormones is of course dependent on their isolation in pure form There is no question but that there is a good deal of overlapping of function of the various fractions Thus they affect not only their specific target glands but exercise metabolic effects not specifically related to the primary effect Our knowledge of the pituitary hormones is still too elementary at present to permit us to determine with any preciseness whether the multiplicity of function of the various hormones represents (*a*) a dosage difference (*b*) a species difference different effects being induced in different experimental species or whether (*c*) the several fractions have not been isolated in a chemically completely pure state or finally (*d*) whether the multiple functions do not actually represent the fields of activity of the various fractions Within recent years several of the anterior pituitary principles have been isolated and separated in a highly purified state from other adenohypophyseal hormones Thus Prolactin (lactogenic hormone) was isolated by Riddle Bates and Dykshorn[3 4] while White Catchpole and Long[5] actually obtained a crystalline protein having the biologic effects of Prolactin from a highly purified preparation of the lactogenic hormone Another of the gonadotropic fractions the interstitial cell stimulating (luteinizing) hormone was isolated in pure form by Shedlovsky and his coworkers[6] The follicle stimulating fraction of the gonadotropic hormones was obtained in a highly purified although not completely pure state by Greep van Dyke and Chow[7] The above authors refer to the follicle stimulating fraction as thylakentrin while the luteinizing fraction is referred to as metakentrin The adrenocorticotropic hormone has recently been isolated in a highly purified if not completely pure form by two groups of investigators Li Simpson and Evans[8] succeeded in isolating this fraction from sheep pituitary while Sayers White and Long[9 10] obtained the hormone from hog glands These highly purified fractions are appreciably free of gonadotropic and thyrotropic effects and exercise only barely appreciable growth and lactogenic effects No chemically pure thyrotropic factor has been isolated although Janssen and Loeser[12] succeeded in obtaining a highly active preparation of thyrotropic hormone in a stable dry form All available thyrotropic fractions possess some gonadotropic activity This is particularly true of the luteinizing effect of thyrotropic factor

There has been a good deal of discussion regarding the actual existence of a 'growth hormone' In general the most highly purified growth promoting fractions have been shown to exercise adrenocorticotropic thyrotropic and lactogenic effects Recently however Li and Evans[13] have succeeded in isolating a highly active and purified growth fraction from the hypophysis of the ox They claim this fraction to be a single and separate hormone and free of lactogenic thyrotropic adrenocorticotropic and gonadotropic effects

The Chemistry and Physiologic Activity of the Hormones of the Adenohypophysis —*The Pituitary Gonadotropic Hormones* —The gonadotropic hormones consist essentially of three fractions the follicle stimulating

hormone (FSH or thylakentrin or Prolan) the luteinizing hormone (interstitial cell stimulating hormone ICSH or metakentrin) and the lactogenic hormone (Prolactin)

The follicle stimulating hormone according to Chow[1] is a glycoprotein with an isoelectric point at about pH 4 8 It is essential for the growth of graafian follicles in the female while it stimulates spermatogenesis and enlargement of the seminiferous tubules of the testes in the male

The luteinizing hormone according to Shedlovsky and his coworkers[6] is also a glycoprotein with a molecular weight of about 90 000 with an isoelectric point at pH 7 45 An analysis of the pure hormone according to the above authors shows that it consists of 49 37 per cent of carbon 6 83 per cent of hydrogen 14 93 per cent of nitrogen and 0 93 per cent of ash The luteinizing fraction described by Shedlovsky and his group was obtained from fresh swine pituitary The fraction studied by Li Simpson and Evans[15] was isolated from acetone dried sheep pituitary and was also a glycoprotein but was found to have a molecular weight of 40 000 and an isoelectric point at pH 4 6 The luteinizing hormone stimulates the interstitial tissue of the testis and ovary It causes formation of the corpora lutea provided that maturing follicles are present and it is essential for the secretion of estrogens from the ovarian follicles It causes a significant increase in the weight of the anterior lobe of the prostate probably due to stimulation of the interstitial tissue of the testicle with elaboration of androgen[6,16]

Prolactin is included with the gonadotropic hormones because it plays a role in maintaining the corpora lutea in a functional secretory state This has been demonstrated by Evans and his coworkers[17,18,19] who have pointed out that extracts containing the lactogenic factor favored placentoma formation in normal hypophysectomized and adrenalectomized rats but not in ovariectomized animals Since placentoma formation is essentially an index of corpus luteum function prolactin must therefore be included among the gonadotropic factors Under the influence of luteinizing hormone alone the corpus luteum would rapidly regress while its secretory state is maintained upon the addition of the lactogenic hormone In addition prolactin causes crop gland proliferation in pigeons and initiates lactation in mammary glands possessed of alveolar development Lactation does not occur however simply as a function of prolactin alone but apparently requires the synergistic action of both prolactin and the adrenal cortex[20,21] There are several general actions of prolactin which are of considerable interest Thus Riddle and Bates have demonstrated the calorigenic effect of prolactin on normal hypophysectomized and thyroidectomized pigeons and doves The lactogenic hormone too apparently has a marked diabetogenic effect in both birds and mammals The glycosuric effect is elicited in normal animals and in hypophysectomized depancreatized cats although not in adrenalectomized cats Houssay and LeLoir however have obtained a characteristic response in adrenalectomized toads and dogs

Prolactin like the other anterior pituitary hormones is a protein although apparently free of carbohydrates The crystalline protein obtained from a highly purified preparation of prolactin has an isoelectric point at

would, theoretically therefore, cast some doubt on the separateness and singleness of a growth factor elaborated by the pituitary gland.

The ultimate proof of the existence of these various fractions as separate and individual hormones is of course dependent on their isolation in pure form. There is no question but that there is a good deal of overlapping of function of the various fractions. Thus they affect not only their specific target glands but exercise metabolic effects not specifically related to the primary effect. Our knowledge of the pituitary hormones is still too elementary at present to permit us to determine with any preciseness whether the multiplicity of function of the various hormones represents (*a*) a dosage difference, (*b*) a species difference, different effects being induced in different experimental species, or whether (*c*) the several fractions have not been isolated in a chemically completely pure state, or finally (*d*) whether the multiple functions do not actually represent the fields of activity of the various fractions. Within recent years several of the anterior pituitary principles have been isolated and separated in a highly purified state from other adenohypophyseal hormones. Thus Prolactin (lactogenic hormone) was isolated by Riddle, Bates and Dykshorn,[3,4] while White, Catchpole and Long[5] actually obtained a crystalline protein having the biologic effects of Prolactin from a highly purified preparation of the lactogenic hormone. Another of the gonadotropic fractions, the interstitial cell stimulating (luteinizing) hormone was isolated in pure form by Shedlovsky and his coworkers.[6] The follicle stimulating fraction of the gonadotropic hormones was obtained in a highly purified although not completely pure state by Greep, van Dyke and Chow.[7] The above authors refer to the follicle stimulating fraction as thylakentrin while the luteinizing fraction is referred to as metakentrin. The adrenocorticotropic hormone has recently been isolated in a highly purified if not completely pure form by two groups of investigators. Li, Simpson and Evans[8] succeeded in isolating this fraction from sheep pituitary while Sayers, White and Long[9,10] obtained the hormone from hog gland. These highly purified fractions are appreciably free of gonadotropic and thyrotropic effects and exercise only barely appreciable growth and lactogenic effects. No chemically pure thyrotropic factor has been isolated although Janssen and Loeser[11] succeeded in obtaining a highly active preparation of thyrotropic hormone in a stable dry form. All available thyrotropic fractions possess some gonadotropic activity. This is particularly true of the luteinizing effect of thyrotropic factor.

There has been a good deal of discussion regarding the actual existence of a growth hormone. In general the most highly purified growth promoting fractions have been shown to exercise adrenocorticotropic, thyrotropic and lactogenic effects. Recently, however, Li and Evans[12] have succeeded in isolating a highly active and purified growth fraction from the hypophysis of the ox. They claim this fraction to be a single and separate hormone and free of lactogenic, thyrotropic, adrenocorticotropic and gonadotropic effects.

The Chemistry and Physiologic Activity of the Hormones of the Adenohypophysis.—*The Pituitary Gonadotropic Hormones.*—The gonadotropic hormones consist essentially of three fractions: the follicle stimulating

in the media of *in vitro* cultures of cells from human placenta. The gonadotropic factor present in the urine during pregnancy has its origin, therefore, in the placenta and is referred to as *chorionic gonadotropic factor*, as distinct from pituitary gonadotropin. The *Aschheim-Zondek test for pregnancy* is based on the urinary excretion of chorionic gonadotropins. Chorionic gonadotropins begin to appear in the urine when the ovum becomes attached to the endometrium of the uterus, that is, at the very beginning of placental formation.[31,32] The maximum urinary concentration of chorionic gonadotropic factor is reached within approximately two months after the first day of the last menstrual period[33] and thereafter begins to fall until it attains a fairly constant level which is maintained until the end of pregnancy. Within seventy-two to ninety-six hours after parturition the chorionic gonadotropic factor has entirely disappeared from the urine.[34]

Chorionic gonadotropin, although not yet obtained in a chemically pure state, is nonetheless chemically and pharmacologically distinct from pituitary gonadotropin. The active principle of the former is also probably a glycoprotein with a molecular weight between 60 000 and 80 000.[35] The chorionic gonadotropin apparently consists mainly of LH, since it merely causes thecal luteinization in the ovaries of hypophysectomized immature rats and does not bring about follicular maturation or formation of corpora lutea,[36] although it does prolong the activity of preformed corpora lutea. In the female it produces depletion of estrogen levels, while in the male it is capable of stimulating the interstitial tissue of the testes, thereby causing an increase in androgen formation.[35] In a general way, pituitary gonadotropins are capable of restoring the ovaries in hypophysectomized rats to an approximately normal state, while chorionic gonadotropin simply produces luteinization.[37] Similarly, pituitary gonadotropin will induce ovulation in the normal rabbit much more readily than will chorionic gonadotropic factor, and the former will cause a much more marked increase in ovarian size than will the latter.[38,39]

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pH 5 65 The crystalline protein contains 51 11 per cent carbon, 6 76 per cent hydrogen 14 38 per cent nitrogen 2 00 per cent sulphur, 5 7 per cent tyrosine 1 3 per cent tryptophane, and 3 4 per cent cystine[6 23]

The pituitary gonadotropins, that is the FSH and the LH factors, are excreted by the kidneys In women during the reproductive period, the urinary excretion of the gonadotropins varies considerably during the menstrual cycle reaching a maximum excretory peak just preceding ovulation[24] The formation and excretion of gonadotropins continues even after the onset of the menopause[25] and after castration in both men and women[6] The gonadotropin formed under such circumstances is different from that which obtains in normal individuals in that the former contains predominantly FSH and relatively little LH

The two pituitary gonadotropic factors augment each other's physiologic effects in a way which neither can achieve alone This augmentary effect was originally pointed out by Hisaw, Fevold and Greep[27] The injection of FSH into normal twenty two-day-old female rats results in ovarian follicular development with considerable increase in size of the ovaries During the early days of such injection no luteinization is evident However, if the injections are continued beyond ten days luteinization occurs This luteinizing effect is due to stimulation of the animals own hypophysis by the FSH, since such luteinization does not occur with the injection of FSH into the hypophysectomized rat On the other hand when FSH and LH are combined and injected into normal twenty-two-day-old rats, the ovaries attain a much greater weight than when FSH is given alone This marked increase in ovarian size cannot be explained by luteinization alone since this augmentary effect can be elicited by the addition of such small quantities of LH to the FSH as not to induce any luteinization These results apply both to the normal and to the hypophysectomized rat A similar augmentary effect is noted in relation to ovulation Thus Hisaw and his group[7] showed that while FSH equivalent to 75 to 100 mgm of pituitary powder is required to induce ovulation in the oestrus adult rabbit and 25 mgm of an LH preparation is required to produce a similar effect a mixture of 15 mgm of FSH plus 1 mgm of LH is found to induce maximum ovulation This dosage is far below the minimal ovulating dose of either hormone alone

Chorionic Gonadotropic Factor —In addition to the pituitary there are several other sources of gonadotropins Evans and Simpson[8] noted that although the pituitary is increased in size during pregnancy and there is an increase in the urinary output of gonadotropins the actual gonadotropic content of the pituitary as determined by pituitary implants in immature animals was extremely small It was later demonstrated that actually the pituitary had little or no gonadotropic activity during pregnancy It became evident, therefore that the large amount of gonadotropic factor excreted in the urine during gestation had its origin elsewhere than in the hypophysis A short while later Collip and his group[29 30] demonstrated the existence of gonadotropic hormone in extracts of human placenta These observations were subsequently confirmed by many investigators Jones and his coworkers[31] provided direct evidence of the formation of gonadotropin by the placenta by demonstrating the existence of this factor

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Chorioepithelioma and Seminoma are a source of gonadotropin in the urine. Chorioepitheliomas in women and men and seminomas of the testicle yield considerable amounts of urinary gonadotropic factor and thus account for the positive Aschheim-Zondek test uniformly found in these patients.[40,41,42] In women a positive Aschheim-Zondek test persisting after the uterine expulsion of the products of conception should raise the possibility of the existence of a chorioepithelioma. During pregnancy it is difficult to establish the diagnosis of chorioepithelioma on the basis of the amount of gonadotropic factor excreted in the urine since in both instances the amount thus excreted may be considerable. However excessive urinary excretion of this factor should make one suspect the possibility of its existence. Occasionally a *teratoma* of the testicle will cause an increased urinary excretion of gonadotropins probably because of the presence of some chorionic tissue in the tumor.[43,36] The amount of gonadotropin excreted in the urine bears very little relationship to the size of the tumor. The gonadal tumor may be so small as to be overlooked but nevertheless may cause a high urinary excretion of gonadotropin. Fortner and Owen[44] suggested that the quantitative determinations of urinary gonado-

tropin can be used for the clinical differentiation between teratomas and chorioepitheliomas. Thus these authors find that normal males excreted 50 mouse units or less of gonadotropin per liter of urine. Patients with teratoma excreted between 50 and 10 000 mouse units per liter of urine while those with chorioepitheliomas excreted from 10 000 to 150 000 mouse units or more per liter of urine.

The gonadotropin producing tumors in the male whether they originate in the testes or elsewhere not infrequently produce gynecomastia with secretion of colostrum.[45]

It has been assumed that the urinary gonadotropin occurring in these tumors is identical with pregnancy chorionic gonadotropin since the pituitaries of patients with chorioepithelioma show histological changes similar to those observed in pregnancy[45] and since the gonadotropic factor in these instances is formed by chorion like tissue. Evans and his coworkers[46] however have demonstrated that such gonadotropic factor consists predominantly of FSH.

The Serum of Pregnant Mares contains gonadotropic factor which is different from both the human pituitary gonadotropin and from chorionic gonadotropin. It is also probably a glycoprotein but with a molecular weight much greater than either pituitary or chorionic gonadotropic factor. It is similar to pituitary gonadotropin but unlike chorionic gonadotropin in that it is capable of producing follicle development in the hypophysectomized female monkey. It differs from pituitary gonadotropin in that is it incapable of inducing spermatogenesis in the hypophysectomized male monkey.[35] The gonadotropin present in the serum of pregnant mares is not excreted in the urine unlike that of both pituitary and chorionic gonadotropin.[47] Burrows[36] has demonstrated that human chorionic gonadotropin when injected into the blood stream of pregnant mares appears in the urine. However gonadotropin from the blood of a pregnant mare when injected into the circulation of a monkey rabbit rat or gelding does not appear in the urine.

Yeast Extract has been demonstrated by Hisaw, Fevold and Greep[7] to exercise some gonadotropic effect. Thus these investigators found that a water soluble substance extracted from brewers yeast was capable of causing enlargement of the testicles of both hypophysectomized rats and immature pigeons. Such extracts will prevent testicular atrophy in rats and will maintain spermatogenesis for a considerable time after hypophysectomy. These preparations however have no effect on the ovaries of immature rats.

Factors Influencing the Secretion of Pituitary Gonadotropin. — The major extra pituitary factors which influence pituitary gonadotropic secretion are the gonads and their hormones. Following removal of the gonads of both male and female experimental animals there occurs a considerable increase in the size of the pituitary of the castrated animal.[35] This increase in size is associated with histological changes in the pituitary already described in the previous chapter. After castration there occurs a marked increase in the gonadotropic potency of the pituitary while the character of the gonadotropic factor is now altered so that it is predominantly FSH with very little LH the latter eventually disappearing entirely. This ap-

plies not only to the experimental animal but also to members of the human species. Thus Zondek[49] observed an increase in the urinary excretion of FSH in both castrated men and women.

The experimental demonstration of the enhancing effect of castration on pituitary potency was first made by Engle[50] and by Evans and Simpson.[51] Engle removed the gonads of male and female rats, some of which varied in age between twenty and thirty days while the remainder were over one year at the time of operation. Several months after castration the rats were killed and their pituitaries were implanted into immature female mice and rats. The results on the size of the ovaries of the implanted rats and mice were compared with controls of pituitary implants from normal rats. It was found that the ovaries of the animals implanted with the pituitaries of the gonadectomized rats were considerably larger than those of the controls. Evans and Simpson[51] performed similar experiments with male rats rendered cryptorchidic and found that cryptorchidism also caused an increase in gonadotropic potency of the pituitary, although not quite so marked as that which occurred in completely gonadectomized animals. The gonadotropic potency of the pituitary is equally influenced by castration of the animal before it has become sexually mature.[6, 53]

Experimental partial castration, that is, where one ovary or one testicle is removed, cryptorchidism, or x-ray sterilization causes enlargement of the hypophysis associated with the same histological changes as are observed after total gonadectomy. Similarly, such incomplete procedures lead to an increase in FSH, although neither the pituitary changes nor the increase in gonadotropin is as marked as occurs with complete castration. The fact that removal of one ovary is followed by a compensatory increase in size of the other ovary, due primarily to the marked increase in follicular development of the remaining gonad, would suggest that in the female the ovarian follicles or the corpora lutea are the ovarian areas which influence the gonadotropic secretory ability of the pituitary. In the male the seminal epithelium of the testicle probably exercises a similar role. This concept is supported by the fact that after x-ray sterilization and cryptorchidization there occurs atrophy of the seminal epithelium of the testis, while the interstitial testicular tissue remains relatively intact.[36]

The direct antithesis of these experiments are the results obtained following the injection of gonadal hormones. Both estrogens and androgens cause a marked reduction in the production of pituitary FSH. The immediate effect of estrogen is to suppress the formation of FSH while causing an increased output of LH, but continued injection finally causes a suppression of the latter too.[57] Meyer and his coworkers[54, 55] conducted studies in castrated adult male and female rats. One group was given estrin daily for approximately a month, while the other group of castrated animals were left untreated and used as controls. The rats of both groups were subsequently killed and the pituitaries implanted into immature rats. It was found that the ovaries of the rats which had been implanted with the pituitaries of the estrin treated castrated rats were only one third as large as those implanted with the pituitaries of the non treated castrates. In the light of previous studies it is clear that these results are due to suppression of the FSH activity of the pituitary. Frank and Salmon[56] made some

interesting observations on gonadectomized, x ray treated, and menopausal women Following injections of estrone in these women there occurred a rapid disappearance of urinary gonadotropin This effect lasted from four to ten weeks after treatment with estrone was discontinued Similar observations, but of a more direct character were made by Rowlands and Sharpey-Schafer,[58] who implanted the pituitaries of 4 women treated with estradiole before death into hypophysectomized female rats The pituitaries of 5 women who were not treated with estradiole before death were implanted into similar animals which were used as controls The effects of the implanted pituitaries on the ovaries and uterus of the hypophysectomized rats were then determined and it was found that the pituitaries of the women treated with estradiole contained much less gonadotropic activity than did those of the untreated women

Essentially the same results were obtained with androgens Moore and Price[59] treated rats with repeated injections of androsterone and then implanted their pituitaries into immature female rats They found that the pituitary gonadotropin of the androgen treated rats was considerably less than that of the untreated controls Similar results were obtained by Hertz and Meyer[60] who established parabiosis between immature female rats and castrated male rats The increased pituitary gonadotropin of the latter caused enlargement of the ovaries of the parabiotic females However if testosterone or dehydroandrosterone was injected into the castrated male animals no ovarian enlargement occurred

Progesterone, the specific hormone of the corpus luteum similarly suppresses pituitary gonadotropin[61]

The parenteral administration of *gonadotropin* causes a reduction in the amount of gonadotropic factor formed by the hypophysis This effect however is elicited only in animals with intact gonads[6, 62] The effect of the injections of gonadotropic factor therefore is to stimulate the gonads with the production of excessive amounts of gonadal hormones which in turn suppress the gonadotropic activity of the pituitary[63] In the castrated animal, injections of gonadotropic factor produce no change in pituitary activity

Bilateral *adrenalectomy* in the rat results in a reduction of pituitary gonadotropic factor[64, 65] The ovaries are very much reduced in size and contain solid masses of corpora lutea Substitutive therapy with pituitary gonadotropin in such animals results in maturation of the follicles and resumption of normal oestral cycles

The influence of the *thyroid* on pituitary gonadotropic factor is not entirely clear The studies of Evans and Simpson[66] would tend to indicate that operative removal of the thyroid results in a reduction in the formation of pituitary gonadotropin while the feeding of fresh thyroid tissue to normal rats results in a slight increase in the formation of this factor

There are several non hormonal factors which affect the amount of pituitary gonadotropin formed Thus *chronic underfeeding* results in a decrease in the size of the pituitary with a reduction in its gonadotropic potency[38] Actually, such semi starvation causes a reduction in size of all the endocrine glands, probably due to a decrease in formation of all anterior pituitary hormonal fractions *Vitamin B complex* deficiency also

reduces the gonadotropic potency of the pituitary body probably due to direct action on the gland. On the other hand *Vitamin F* deficiency at least in the male results in an increased formation of FSH and a decreased formation of LH by the anterior pituitary. This effect of vitamin F deficiency is meditated essentially through the testis in that such a lack injures the latter organs and hence exercises an effect similar to that of castration on the pituitary. In female animals unlike in males vitamin F deficiency directly injures the pituitary and thus depresses its gonadotropic potency.[36]

The Adrenocorticotropic Factor.—The adrenocorticotropic hormone of the anterior pituitary acts on its target gland the adrenal cortex. It has been isolated in a highly purified state by two groups of independent investigators. Li, Simpson and Evans[8] employing a salt fractionation technique isolated this fraction from sheep pituitary, while Sayers, White and Long[9,10] obtained with isoelectric precipitation an identical fraction from hog pituitary. Both found the hormone to be a protein with a molecular weight of approximately 20,000 and an isoelectric point between 4.7 and 4.8. Both reported essentially the same percentage of carbon, hydrogen, nitrogen and sulphur. The hormone is stable in a buffered solution at pH 7.5 even at 100° C. It is readily destroyed by relatively weak alkaline solutions, by trichloracetic acid and by tryptic digestion. It is quite stable in a 0.1 molar solution of HCl. It readily precipitates in the presence of 20 per cent sulfosalicylic acid, 20 per cent trichloracetic acid and in 5 per cent lead acetate.

The early recognition of the relation of the adrenal cortex to the hypophysis was essentially a clinical one. Falta[67] observed extensive atrophy of the adrenal cortex in association with destructive lesions of the anterior lobe of the hypophysis. Subsequently hypoplastic adrenals were noted in pituitary dwarfism[68] and in Simmonds' cachexia.[9] Early experimental studies definitely established the fact that total hypophysectomy resulted in a rapid atrophy of the adrenal cortex in a variety of animals including the dog.[70,71,72,73] The atrophy is limited essentially to the cortex, the medulla remaining unaffected.[70,74] The cells of all three zones of the cortex show a diminution in the amount of cytoplasm. The atrophic process begins in the reticular zone and eventually involves the fascicular layer and finally the entire cortex. When the process is complete, the cells are small and distorted, the reticular layer is unrecognizable, while the fascicular layer has completely lost its cord-like arrangement of cells. In addition, the Golgi apparatus has shrunken and the lipoid granules have practically disappeared except from the middle portion of the cortex where some are still present. These atrophic adrenals can be almost completely restored to their normal histological structure by daily homotransplants of the pituitary gland[70] or by the use of adrenocorticotropic pituitary extracts.[71,72,75,76] One further point of interest in this respect is the relationship between the pituitary and the compensatory hypertrophy of the remaining adrenal in the unilateral adrenalectomized animal. In the intact animal, the removal of one adrenal is promptly followed by a compensatory increase in size of the cortex of the remaining adrenal. This phenomenon does not occur in the hypophysectomized animal. However

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to those obtained following the use of adrenocorticotropic hormone under identical experimental conditions. The difference between the two lies perhaps in their respective effects on muscle glycogen in that the adrenal cortical hormone is not as capable of inducing and maintaining as high a level of muscle glycogen as is the pituitary hormone. This would represent an effect of the latter exercised independently of the adrenal cortex.

In the hypophysectomized-depancreatized animal the administration of adrenocorticotropic hormone will result in an increase in the blood sugar level with a consequent glycosuria. Long and Lukens[91] have suggested that this effect may in part at least be mediated through the adrenal cortex. In support of this hypothesis Lukens and Dohan[97] have demonstrated an increase in the glycosuria, urinary nitrogen excretion and blood sugar level following the administration of cortical extract to hypophysectomized depancreatized animals. This problem was approached in a somewhat different fashion by Houssay and Biasotti[93] who found that if adrenalectomized-depancreatized dogs are treated with adequate amounts of cortical extract the blood sugar level is increased. However, if in addition anterior pituitary extract is administered there occurs a further considerable elevation of the blood sugar level. It is interesting that no exacerbation of the diabetes occurred in such animals following the administration of anterior pituitary extracts alone.[94]

Finally, the close relationship between the adrenal cortex and the adenohypophysis on carbohydrate metabolism is evidenced by the amelioration of total pancreatic diabetes by both hypophysectomy[95] and bilateral adrenalectomy.[92] The various experimental observations would suggest that the adenohypophysis influences carbohydrate metabolism through at least two channels: (a) through the stimulating action of the adrenocorticotropic hormone on the adrenal cortex, and (b) through the elaboration of another factor or factors which act directly on the tissues.[90] The adrenocorticotropic hormone stimulates the secretion of cortical adrenal hormones. The hormones in turn increase the catabolism of proteins and their conversion into glucose. The hypophysectomized animal, like the adrenalectomized one, is extraordinarily sensitive to insulin. The anti-insulin or glycotropic effect of adrenocorticotropic hormone parallels the action of some of the adrenal cortical fractions, notable those of the corticosterone and 17-hydroxy-11-dehydrocorticosterone type. Jensen and Grattan[96] have suggested that the glycotropic action of the pituitary is mediated through the effect of the adrenocorticotropic hormone on the adrenal cortex.

The Diabetogenic Principle.—To date no pure diabetogenic principle has been isolated from the anterior pituitary body. The suspicion of the existence of such a factor is based essentially on the behavior of crude anterior pituitary extract in respect to carbohydrate metabolism which is somewhat different from that of purified adrenocorticotropic hormone. The daily injection of crude anterior pituitary extract induces hyperglycemia and glycosuria. This effect is readily produced even in the absence of the adrenals and in this respect is different from the action of adrenocorticotropic factor.[97] This effect of the diabetogenic factor is especially striking in the animal maintained on a high carbohydrate diet, although it

is also evident in animals on a normal diet [99] However in the fasting animal the diabetogenic effects are remarkably reduced [99] The continuous injection of progressively increasing amounts of the crude extract eventually results in the production of a permanent diabetic state in the susceptible animal, despite the discontinuance of the injections In such animals there occurs a depression of the respiratory quotient and a characteristic glucose tolerance curve [100] The injection of relatively small amounts of crude anterior pituitary extract eventually results in a state of refractoriness which can be overcome by increasing the dosage

The diabetogenic effect of the crude anterior pituitary extract is probably dependent in part at least on the effects of such extracts on the histology of the islet cells of the pancreas Richardson[101] has demonstrated that the pancreas of animals treated with such fractions contains less insulin than normal The islet cells show considerable degeneration with degranulation and hydropic degeneration with eventual hyalization of the islets

The possible existence of a diabetogenic factor raises the inevitable question concerning the relation of the adenohypophysis to pancreatic function and the possible existence of a *pancreatropic* hormone Experimental reports concerning these points have been contradictory and confusing Koster[102] found that hypophysectomy in dogs results in pancreatic atrophy while von Bakay[103] described an increase both in size and number of the islands of Langerhans in these animals Anselmino and Hoffman[104] prepared anterior pituitary extracts *ostensibly free of gonadotropic and thyrotropic effects* which produced hypertrophy and hyperplasia of the pancreatic islets when injected into dogs Associated with these histological changes there occurred a decrease in the blood sugar level Richardson and Young [105] employing crude anterior pituitary extracts induced similar histological changes in the pancreas of rats This same extract however when injected into dogs produced glycosuria and permanent diabetes This species difference becomes even more pronounced when measured in terms of insulin content of the pancreas of the experimental animal The injection of anterior pituitary extracts in dogs causes a marked decrease in the insulin content of the pancreas [106] whereas the injection of similar extracts into rats increases the pancreatic insulin both in the intact and the hypophysectomized animal [107 108]

No definite conclusions can be drawn at present concerning the existence of a pancreatropic hormone A more definitive answer must await the possible isolation of this fraction in pure form

Finally the injection of crude alkaline or saline anterior pituitary extracts produces an increase in *ketone* bodies both in the blood and urine This *ketogenic effect* is most pronounced in animals which are fasted or fed diets rich in fat The ketogenic factor is apparently distinct and separable from the diabetogenic fraction [109]

The Thyrotropic Hormone — A chemically pure thyrotropic hormone has not as yet been isolated Ciereszko and White[110] have conducted extensive studies on the fractionation and isolation of the thyrotropic hormone from beef hypophyses Their thyrotropic fraction is a protein molecule having an approximate molecular weight of 10 000 with a nitrogen content of 12 4 per cent and a carbohydrate content of 3 5 per cent The final

to those obtained following the use of adrenocorticotropic hormone under identical experimental conditions The difference between the two lies perhaps, in their respective effects on muscle glycogen in that the adrenal cortical hormone is not as capable of inducing and maintaining as high a level of muscle glycogen as is the pituitary hormone This would represent an effect of the latter exercised independently of the adrenal cortex

In the hypophysectomized-depancreatized animal the administration of adrenocorticotropic hormone will result in an increase in the blood sugar level with a consequent glycosuria Long and Lukens[91] have suggested that this effect may in part at least be mediated through the adrenal cortex In support of this hypothesis Lukens and Dohan[92] have demonstrated an increase in the glycosuria urinary nitrogen excretion and blood sugar level following the administration of cortical extract to hypophysectomized-depancreatized animals This problem was approached in a somewhat different fashion by Houssay and Biasotti[93] who found that if adrenalectomized-depancreatized dogs are treated with adequate amounts of cortical extract the blood sugar level is increased However if in addition anterior pituitary extract is administered there occurs a further considerable elevation of the blood sugar level It is interesting that no exacerbation of the diabetes occurred in such animals following the administration of anterior pituitary extracts alone[94]

Finally the close relationship between the adrenal cortex and the adenohypophysis on carbohydrate metabolism is evidenced by the amelioration of total pancreatic diabetes by both hypophysectomy[95] and bilateral adrenalectomy[95] The various experimental observations would suggest that the adenohypophysis influences carbohydrate metabolism through at least two channels (a) through the stimulating action of the adrenocorticotropic hormone on the adrenal cortex and (b) through the elaboration of another factor or factors which act directly on the tissues[90] The adrenocorticotropic hormone stimulates the secretion of cortical adrenal hormones The hormones in turn increase the catabolism of proteins and their conversion into glucose The hypophysectomized animal like the adrenalectomized one is extraordinarily sensitive to insulin The anti insulin or glycotropic effect of adrenocorticotropic hormone parallels the action of some of the adrenal cortical fractions notably those of the corticosterone and 17 hydroxy 11-dehydrocorticosterone type Jensen and Grattan[96] have suggested that the glycotropic action of the pituitary is mediated through the effect of the adrenocorticotropic hormone on the adrenal cortex

The Diabetogenic Principle —*To date no pure diabetogenic principle has been isolated from the anterior pituitary body The suspicion of the existence of such a factor is based essentially on the behavior of crude* anterior pituitary extract in respect to carbohydrate metabolism which is somewhat different from that of purified adrenocorticotropic hormone The daily injection of crude anterior pituitary extract induces hyperglycemia and glycosuria This effect is readily produced even in the absence of the adrenals and in this respect is different from the action of adrenocorticotropic factor[97] This effect of the diabetogenic factor is especially striking in the animal maintained on a high carbohydrate diet although it

after the beginning of injections the basal metabolic rate has returned to the control level and frequently falls considerably below this level There occurs an involution of the thyroid hyperplasia and a reaccumulation of acinar colloid and the exophthalmos disappears The serum obtained from such animals during the refractory phase is capable of neutralizing the effect of thyrotropic factor injected into previously untreated animals[128]

The refractory phase exhibited by the treated animal is due to the development of an inhibitory substance referred to as an antihormone in this instance it is an antithyrotropic factor Similar antihormones are observed to occur following the injection of gonadotropic diabetogenic and ketogenic substances as well as after the use of prolactin and "growth promoting factor"[129] Each antihormone is specific for the particular factor used in its production Thus antithyrotropic factor exercises no effect on gonadotropic hormones etc

The nature of the antihormones is not entirely clear but there is considerable evidence to indicate that it is probably an antibody produced as a response to the foreign protein content of the hormone used Thus antithyrotropic substance shows considerable species specificity since rabbits and guinea pigs refractory to bovine thyrotropic extract will still respond to pig thyrotropic factor[130] Werner[131] has succeeded in preparing a purified thyrotropic factor by precipitation with flavianic acid which may be administered for long periods of time without the development of a refractory state However the presence of an antithyrotropic factor in minute amounts has been described in the serum of normal untreated members of various species[129,132] The nature of this factor and its identification with true antithyrotropic factor has not been established

The antithyrotropic factor as well as the other antihormones is formed readily in hypophysectomized and also in thyroidectomized or gonadectomized animals[129] The antithyrotropic factor is apparently associated with a serum globulin[133] and is readily destroyed by boiling[128]

The clinical significance of the antihormones is obvious The prolonged use of any adenohypophyseal fraction will result in the development of a refractory state during which the therapeutic value of the hormone employed is entirely lost If we are to judge from experimental studies on animals this refractory phase may continue for many months

Factors Conditioning Thyrotropic Response —Soffer and his coworkers[134] found that following the injection of epinephrine in-oil into normal dogs there occurred marked hyperplasia of the thyroid which reached its peak within six days and then began to subside That this was not due to the direct effect of the epinephrine on the thyroid gland itself was evidenced by the fact that the serum of totally thyroidectomized dogs similarly treated contained large quantities of circulating thyrotropic factor This serum injected into immature guinea pigs produced marked hyperplasia of the thyroids of these animals Teitelbaum and Uhlenhuth[135] had previously found that adrenalin or pilocarpin when given together with thyrotropic factor enhanced the effect of the latter

Adrenalin not only stimulates the anterior hypophysis to the secretion of thyrotropic factor but also causes an outpouring of adrenocorticotropic hormone[81] Thus Long and Fry[81] found that subcutaneous or in

product is a white powder soluble in water and precipitated from neutral solutions by acetone in high concentration. One fifth of a microgram of this material injected daily for five days will produce a minimal histological response in the three day-old chick.

Even prior to the isolation of a thyrotropic factor it was known that surgical removal of the hypophysis in the experimental animal resulted in marked thyroid atrophy and decrease in oxygen consumption.[110, 111, 112, 113] Similar observations have been noted clinically in that severe hypothyroidism is always present in patients with Simmonds cachexia. In this disease the thyroid presents the same atrophic process noted in the totally hypophysectomized animal.

Thyrotropic hormone acts on its target gland, the thyroid. Injection of this hormone into a suitable experimental animal results in the production of thyroid hyperplasia and hypertrophy, disappearance of colloid, hypertrophy of the Golgi apparatus of the thyroid gland, an increase in the oxygen consumption, and in some animals a temporary exophthalmos.[114, 115, 116, 117, 118]

The earliest effect following the injection of thyrotropic factor is an increase in intracellular colloid.[119] De Robertis,[119] employing the freezing drying technic, observed this effect to occur as early as fifteen minutes after the administration of the hormone. In view of the large size of the thyroglobulin molecule one could not very well explain this phenomenon on the basis of the migration of this molecule through the cell membrane. De Robertis, however, found a proteolytic enzyme in the colloid of the thyroid follicle which increased in activity with increased stimulation of the thyroid. The appearance of colloid droplets in the acinar cells occurs, therefore, as the result of liquefaction of follicular colloid and its migration into the cell from which it is absorbed into the general circulation. The liquefaction and disappearance of follicular colloid is followed by an increase in the height of the acinar cells, frequently the presence of a considerable increase in mitotic figures, and a decrease in size and distortion of the alveoli. For all intents and purposes, the thyroids of the animals injected with thyrotropic factor closely resemble the thyroids of patients with Graves disease.

Following the injection of thyrotropic hormone there occurs a decrease in the iodine content of the thyroid gland associated with an increase in blood circulating iodine.[120, 121, 122, 123] This phenomenon occurs concomitantly with the liquefaction and absorption of the follicular colloid. In certain experimental animals such as the metamorphosing tadpoles, duck, guinea pigs and rabbits, exophthalmos appears following the parenteral administration of thyrotropic factor.[118, 124, 125, 126] The development of exophthalmos is completely independent of the thyroid gland, since it can be induced experimentally by the injection of thyrotropic factor into the thyroidectomized animal.[127]

The Antihormones.—The injection of thyrotropic factor in a suitable animal is followed by the usual objective and histological evidence of increased thyroid function. The hyperthyroidism reaches a peak within seven to twelve days and then a remission begins to ensue despite the continued administration of thyrotropic hormone. Within three to five weeks

Rawson[138] suggests that this is due to an oxidative reaction which occurs between the thyroid cell and the thyrotropic hormone

There are other factors which influence the amount of thyrotropin formed by the pituitary Collip and Anderson[139] have shown that the exogenous administration of thyrotropic factor decreases the thyrotropic content of the pituitary A similar decrease occurs after castration in the male [140] An increase in thyrotropin in the pituitary has been reported to occur in humans with infectious diseases [141]

The 'Growth Factor' of the Anterior Hypophysis—Considerable controversy has arisen concerning the existence of a specific factor elaborated by the anterior hypophysis capable of stimulating body growth in the normal and hypophysectomized animal As a prerequisite for the existence of such a factor it would be necessary that the hormone be free from any other hormones such as the thyrotropic adrenotropic or gonadotropic hormones which may influence growth in a nonspecific manner The difficulty arises because of the influence of a multiplicity of factors on body growth Thus the course of skeletal growth is determined primarily genetically But there are nutritional and pathologic conditions which are capable of influencing the degree of growth Poor nutrition lack of adequate mineral and vitamin intake, notoriously impede proper physical development Similarly, the lack of growth of the cretin and the dramatic response to thyroid extract or thyroxin does not warrant the assumption that any of these agents represents a specific growth factor

The earliest suspicion that the hypophysis was in some way concerned with the general problem of growth developed from certain clinical observations Towards the latter part of the last century two independent clinical investigators noted the existence of pathological changes in the pituitary in instances of acromegaly and dwarfism [142, 143, 144] Some twenty years later Aschner[145, 146] demonstrated that dwarfism could be produced experimentally in dogs by extirpation of the pituitary gland These findings were subsequently confirmed and extended by American investigators notably Crowe Cushing and Homans [147] Benedict and Homans [148] P E Smith[149] and Allen [150] In 1921 Evans and Long[151] reported the production of gigantism in rats by the daily intraperitoneal injections of extracts of the anterior lobe of beef hypophyses Finally Putnam Benedict and Teel[152] succeeded in producing canine acromegaly by the injection of an anterior pituitary extract similar to that employed by Evans and Long

As a result of these clinical and experimental studies it was definitely established that the anterior hypophysis played an important role in growth Overactivity of the gland led to an increase in body size while the antithesis was true in clinical and experimental underfunction However these observations *per se* did not necessarily imply the existence of a specific anterior hypophyseal factor concerned with growth In the light of the influence of the hypophysis on the thyroid adrenals and gonads it was conceivable that the clinical and experimental results could be explained on the basis of the influence of the anterior pituitary on these target glands However these observations did stimulate the search for a possible fraction concerned exclusively with growth and free from any effects on the other endocrine glands

travenous administration of epinephrine caused a marked fall in adrenal cholesterol and ascorbic acid These latter phenomena are evidence of increased formation of adrenal cortical hormone Since the effect of adrenalin on adrenal cholesterol and ascorbic acid does not occur in the hypophysectomized animal, the assumption is a reasonable one *that the increased adrenal cortical hormone formation is due to excessive* secretion of adrenocorticotropic factor

The fact then that epinephrine can stimulate the anterior hypophysis to the secretion of, at least, thyrotropic and adrenotropic factors suggests that adrenalin either by itself directly or through its action on the sympathetic nervous system plays an important and perhaps even primary role in controlling the functions of the anterior hypophysis

Chen and Van Dyke[136] have demonstrated an increase in the thyrotropic content of rabbit pituitary after total thyroidectomy Rawson and Starr[137] found an increase in circulating thyrotropic factor after total thyroidectomy in man Soffer and his group[134] demonstrated a somewhat lesser increase in blood thyrotropin after subtotal thyroidectomy in man The results of these experiments would indicate that thyroidectomy causes both an actual increase in secretion of thyrotropic factor and an increase in the amount of thyrotropin found in the peripheral blood Two mechanisms are actually involved in the production of these changes As early as 1917 Herring[138] demonstrated that thyroid extract causes a decrease in the size of the rat thyroid The explanation for this probably resides in the fact that thyroid extract depresses the secretion of thyrotropic factor of the anterior pituitary Following thyroidectomy therefore with its consequent reduction in thyroxin formation one would expect an increase in thyrotropin secretion The appearance of thyrotropin in the peripheral circulation in excessive amounts however is not necessarily due to the increased quantities of this hormone secreted Rawson and Starr[137] have observed that in normal individuals very little thyrotropin can be demonstrated in the peripheral circulation while in patients with Graves disease the amount present in the blood is even less These observations were confirmed by Soffer and his coworkers [134] Rawson[139] then showed by means of tissue culture technic that slices of thyroid tissue inactivate thyrotropic hormone, and that such inactivation may be prevented by the addition of sodium iodide to the medium This observer further demonstrated that sodium iodide prevented the action of thyrotropic factor on the thyroid of hypophysectomized rats The clinical counterpart of this was demonstrated by Soffer and his coworkers [134] These observers found that following the administration of Lugol s solution to patients with Graves disease there occurred a considerable increase in circulating thyrotropin

It would seem then, that the thyroid acts as a sponge in taking up almost all of the thyrotropic factor formed by the hypophysis and hence so little appears in the blood Following thyroidectomy the increased amount observed in the peripheral circulation is due both to an increased amount formed as a result of the absence of the depressant effect of thyroid extract, and by the absence of the thyroid which would normally take up the thyrotropin formed The therapeutic effects of iodine are probably due to the fact that it prevents the access of thyrotropin to the thyroid

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During the next decade and a half experimental investigations were directed essentially to a study of the physiologic properties of anterior pituitary extracts loosely referred to as growth hormone [153, 154, 155, 156]. These extracts were crude and unquestionably contained several fractions, some of which were subsequently identified as having thyrotropic, adrenotropic and lactogenic effects. So that as recently as 1935 it was impossible to say as to whether the growth effects elicited by the available anterior pituitary extracts were a function of a specific growth factor or were the result of the better known thyrotropic or lactogenic fractions. In 1935 Dingemanse and Freud[156] prepared a purified growth hormone from beef anterior pituitary, which was reported to be free of thyrotropic and lactogenic effects but which nonetheless exhibited growth effects. In 1936 Evans[157] described a growth fraction prepared from standard alkaline anterior pituitary extract by repeated precipitation with 0.4 per cent saturated ammonium sulfate. This fraction contained only the most minute amounts of thyrotropic and lactogenic hormones.

The controversy as regards the specificity of a growth hormone is in good part related to the work of Riddle and his group [3, 4] who have demonstrated that prolactin and thyrotropin exercise growth effects on suitable animals. Employing "silver dwarf" mice, which is said to be a naturally hypophysectomized animal at least with regard to the growth promoting eosinophils, these investigators found that the administration of either prolactin or thyrotropin was capable of inducing growth. The administration of both hormones together caused even greater growth, a phenomenon which these authors attributed to the synergistic action of the hormones on one another. This synergistic effect is not evident in all species; for example, Riddle found that in pigeons prolactin will induce growth, while thyrotropin will cause actual weight loss. The two together will nullify the effects of the prolactin. The growth promoting factor of the so-called growth hormone Riddle attributes, therefore, to the presence, even in minute quantities, of prolactin and thyrotropin. In an illuminating and vigorous discussion which occurred at a meeting of the "Association for Research and Mental Disease"[157] Riddle pointed out that he had occasion to test the hypophyseal growth hormone of Dingemanse and Freud and found it to contain detectable quantities of both lactogenic and thyrotropic factor. He concluded, therefore, that whatever growth effects growth hormone has must be attributed to the presence of these fractions. The observations of Evans[157] however, lead one to the conclusion that there is a factor in anterior pituitary extracts which exercises an effect on growth which is independent of either prolactin or thyrotropin. Lactogenic hormone of a high degree of purity will not induce growth in the hypophysectomized rat. Similarly, thyrotropic hormone, which is capable of stimulating growth in the thyroidectomized rat, will not exercise the same effect in the hypophysectomized or thyroidectomized hypophysectomized animal. On the other hand, growth hormone will produce a suitable effect in both the hypophysectomized and thyroidectomized animal. Evans explains the growth action of prolactin and thyrotropin obtained by Riddle on the basis of the presence of contaminating growth hormone in the latter's preparations.

It became obvious therefore that the solution of the controversy was dependent on the isolation of a *single substance* from the pituitary capable of stimulating growth. In 1944 Li and Evans[13] reported the isolation of a protein from the anterior lobes of ox pituitaries which behaves as a single substance in electrophoresis with an isoelectric point at pH 6.85 and which causes resumption of body growth in hypophysectomized rats. Employing female rats hypophysectomized at the age of twenty seven days they found that the daily intraperitoneal injection of 0.01 mg of the substance for ten days starting fourteen days after the operation resulted in a 10 gram gain in body weight. On the other hand a total dose of 5.0 mgm did not show lactogenic, thyrotropic, adrenocorticotropic, follicle-stimulating or interstitial cell-stimulating activities. The authors conclude that this product is substantially free of other biologically active pituitary contaminants.

Method of Action of Growth Hormone.—Growth is a complex phenomenon involving many metabolic activities which result in an increase in size and weight. We can loosely accept the latter then as evidence of growth. However this results in certain inaccuracies since we can hardly accept abnormal increases in fat and water such as occurs in obesity and edema for whatever reasons as evidence of growth. We must therefore specifically define the character of the increase in size and weight which will be acceptable as evidence of true growth.

Lee[153] suggests that those metabolic functions which are concerned with an increase in size and weight normally exhibited by young animals be accepted as criteria of the physiology of growth. Similar criteria would be applicable to adult animals. The basic feature of growth in young animals is the manufacture of adequate amounts of protein for the building of new cells. This is manifested chemically by a strongly positive nitrogen balance and the retention of water and electrolytes and by a relatively low body content of fat. These changes are further associated with the fact that the amount of food consumed is large in proportion to the body weight. In the normal course of events when maturity is attained and growth ceases the metabolic status is maintained in equilibrium. The urinary and fecal nitrogen as well as the excretion of water and minerals equals the intake while the intake of food becomes less in proportion to body weight. Normal increases in weight during the growth plateau period of maturity are due essentially to increased deposition of fat. Lee[158] summarizes this process as follows: "The chemical characteristics of those increments of body mass which can be regarded as true growth are a high content of water, protein and mineral salts and a low content of fat."

Experimental studies with a relatively crude anterior pituitary growth hormone demonstrate the phenomenon described above. Using rats for experimental studies under rigidly controlled circumstances Lee[153] found that growth hormone increased the voluntary food intake. In addition the treated animals showed a marked excess in weight gain over their control litter mates despite the fact that the food intake of the former was restricted to that of the latter. During the administration of growth hormone there was a decrease in urinary nitrogen excretion accounted for

mostly by a lessened urea excretion. The urinary excretion of creatinine and uric acid was unaffected, while there was an increased calcium excretion.[154,155] In addition there occurred a 20 to 30 per cent decrease in the non protein nitrogen of the blood due mostly to a decrease in amino acids and urea.[153] Such changes would bespeak the excessive utilization of amino acids for protein building.

This increase in protein formation results not only in a general increase in body size and weight, but is associated with a marked splanchnomegaly. Thus Cushing and Davidoff[159] have noted a remarkable increase in size of the internal organs in human acromegaly, while Putnam, Benedict, and Teel[15] have produced similar results in dogs made acromegalic by treatment with anterior pituitary growth extracts. The antithesis of this is equally true in that splanchnomicria is seen in pituitary dwarfism while atrophy of the visceral organs was observed to occur after hypophysectomy in rats.[160] The effect of growth hormone on the skeletal structure is characterized mainly by an intensification of activity of the periosteal ossification zones of the long bones, proliferation of the cartilage of the epiphyseal disc and in general stimulation of all the normal processes of osteogenesis at the epiphyseal-diaphyseal junction.[161,16,163]

Influence of Other Hormones on Growth Hormone Response of the Anterior Hypophysis.—That estrogens play a role in body size and growth is evidenced by the fact that in most mammals the male is larger than the female. It was early demonstrated that this was in some way related to ovarian function. Steinach and Holzknecht[164] approached this problem by implanting ovaries into castrated young male guinea pigs and testes into spayed female litter mates. In these experiments the males bearing the ovaries failed to attain the general size and weight of normal males or females while the females grafted with testes grew to an unusual size. Somewhat later, Bugbee and Simond[165] demonstrated that repeated injections of follicular extract retarded growth in both normal and castrated male and female rats. This observation has since been amply confirmed. Equally effective as an inhibitor of body growth is the use of synthetic estrogens, such as diethylstilbestrol.[166]

The mechanism of the inhibitory effect of estrogens is not entirely clear. In part at least its effect can be explained on the inhibition of growth hormone formation that results from its use. Thus Reece and Leonard[167] removed the ovaries and pituitaries from immature rats and five days later commenced treatment with pituitary implants daily for eleven days. The implants consisted of pituitaries from normal adult females and males and pituitaries from estrogen treated females and males. The rats receiving pituitary implants from estrogen treated animals gained considerably less in size and weight than did the rats which received implants from non treated animals.

These experiments would suggest that the estrogen therapy had in some way adversely affected the growth promoting action of the pituitaries. That this is not the only explanation, however, is suggested by the studies of Griffiths and Young.[168] These investigators checked the growth of one series of rats by hypophysectomy and another series by the subcutaneous implantation of 15 mgm of a synthetic estrogen. Both groups were then

treated with equal amounts of anterior pituitary extracts It was found that the hypophysectomized animals responded much more favorably to the injection of the anterior pituitary extracts than did the ones implanted with estrogen The estrogens exercise still another effect They hasten osseous union between the epiphyses and the shaft and thus curtail the growth of bones and affect general growth It is impossible to say as to whether this effect is dependent on the influence of the estrogens on the pituitary

Testosterone on the other hand in low or average dosage, tends to stimulate growth essentially through its effect on the pituitary [169] Interestingly enough however there is considerable variation in the results of castration both in man and in lower animals The available reports indicate that following this procedure there may occur either a retardation of growth or an increase in the length of the long bones with a consequent increase in size [96] In man, the administration of testosterone to patients with hypogonadism results in a spurt of growth [170]

The metabolic effects of testosterone are not dissimilar to those observed after the use of anterior pituitary growth hormone There occurs an increase in appetite and a considerable retention of water and electrolytes In addition the urinary and fecal excretion of nitrogen is decreased to less than that of the intake, resulting in a definitely positive nitrogen balance [171 172 173] The increase in body weight following the use of androgens is due essentially to these factors and accounts in good part for the more marked muscularity observed in males as contrasted to females

The thyroid exercises an important effect on growth Young thyroidectomized animals fail to grow properly because of impairment of pituitary function Because of the absence of the thyroid hormone there occurs a reduction in the eosinophilic elements of the adenohypophysis with a consequent decrease in the secretion of growth hormone [162] The administration of growth hormone to such animals will result in a resumption of growth which will become even greater if thyroxin is administered in addition to the growth factor [156]

Hormones of the Posterior Lobe —The separate hormonal fractions of the posterior lobe have not as yet been isolated in a chemically pure state Abel and his associates[174] in 1923 isolated a tartrate of a high degree of purity which manifested pressor oxytocic, and antidiuretic properties Until recently it was the general impression that the pituitary hormones actually consisted of two principles the vasopressor and the oxytocic factors The antidiuretic effect was considered to be simply another function of the vasopressor principle However Heller[175] has demonstrated that the antidiuretic and pressor factors are not identical since heat inactivation of the pressor principle proceeds at a more rapid rate than that of the antidiuretic factor In any event in clinical usage with the factors available today the pressor principle contains or at least exercises an antidiuretic effect among others There is no extract available at present which contains only the antidiuretic factor Neither pressor nor oxytocic hormones have been isolated in crystalline form but highly purified extracts containing one or the other of these have been prepared

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Hormones of the Posterior Lobe —The separate hormonal fractions of the posterior lobe have not as yet been isolated in a chemically pure state Abel and his associates[174] in 1923 isolated a tartrate of a high degree of purity, which manifested pressor oxytocic and antidiuretic properties Until recently it was the general impression that the pituitary hormones actually consisted of two principles the vasopressor and the oxytocic factors The antidiuretic effect was considered to be simply another function of the vasopressor principle However Heller[175] has demonstrated that the antidiuretic and pressor factors are not identical since heat inactivation of the pressor principle proceeds at a more rapid rate than that of the antidiuretic factor In any event in clinical usage with the factors available today the pressor principle contains or at least exercises an antidiuretic effect among others There is no extract available at present which contains only the antidiuretic factor Neither pressor nor oxytocic hormones have been isolated in crystalline form but highly purified extracts containing one or the other of these have been prepared

Recently Van Dyke and his group[176] have isolated a single protein hor-

mone in pure state which possesses pressor, oxytocic, and antidiuretic activities. This protein molecule probably represents the hormone elaborated by the posterior pituitary body. In physiologic activity this molecule is probably broken down into several constituents which manifest separate pharmacologic effects, thus conveying the impression of different hormones elaborated by the gland. This basic posterior pituitary hormone has a molecular weight of 30,000 with an isoelectric point at pH 4.8. The pressor, oxytocic, and antidiuretic activities associated with this posterior pituitary hormone are present in approximately equal amounts: 16.6 units per mgm. for the first two, and 16.4 units per mgm. for the antidiuretic activity. This ratio of activity is identical with that existing in the mother substance of the untreated gland.[177]

The melanophore-expanding principle is elaborated by the pars intermedia of the amphibia.[97] It is very unlikely that this factor is secreted in the human. Although some chromatophore expanding substances have been obtained from human urine, the reaction for these substances is by no means specific and their hypophyseal origin decidedly questionable. In the amphibia, however, the melanophore-expanding principle is distinct from pressor and oxytocic factors, since the latter two fractions can be destroyed by boiling the extract with alkali, which leaves the pigmentary principle intact.[178]

Clinically, the hormones of the posterior lobe are available as "whole posterior pituitary extract," "pitressin," which consists essentially of the vasopressor and antidiuretic principles, and "pitocin," which exercises the oxytocic effect. Both pitressin and pitocin have some pharmacologic effects in common in that they are both capable of inducing hyperglycemia and acting as antagonists to insulin in certain animals.[179,180] Actually the significance of this common effect is dubious, since it is impossible as yet to obtain a commercially available product of either one factor entirely free of contamination with the other.

Pharmacologic Effects of the Vasopressor (Pitressin) Substance.— Pitressin exercises effects on the cardiovascular system, the kidneys, and on the intestinal tract. In addition, both pitressin and pitocin exercise certain metabolic effects. The nature of the pharmacologic action of pitressin is considerably dependent on the animal used, the type of anesthesia employed, the size of the dose, and the mode of administration. None of the posterior pituitary principles are effective when administered orally, and in general repeated doses parenterally administered become progressively less effective.

In man, neither posterior pituitary liquid nor pitressin causes an appreciable rise in blood pressure.[181] Actually the effect in man varies considerably in that some individuals may show a brief moderate increase, while others will show a definite decline, and in most there will be no demonstrable effect.[18] However, there does occur a fall in pulse rate, a decrease in oxygen consumption, and a decrease in cardiac output. The decrease in cardiac output is due largely to constriction of the coronary vessels.[18] In experimental animals, however, the blood pressure effect is determined by the species of animal employed, the type of anesthesia used, the size of the individual dose, and the time interval between injections. Small doses

given to etherized cats or dogs will produce a sharp rise in blood pressure which may last for fifteen to thirty minutes. Frequent repetition of this dose to the same animal will result in a progressively lesser effect. Large doses given to normal or anesthetized dogs or cats will induce an initial fall in pressure followed by a rise.[154] In the urethanized rabbit injected with a small dose there occurs a rise in blood pressure which lasts for only a few seconds, followed by a drop and then a secondary rise.[8]

The pressor effect of pitressin is due to the action of the hormone on the musculature of the blood vessels and is not antagonized by nicotine or severance of the brain or spinal cord.[97] The coronary vasoconstrictor effect of the hormone, however, may be obviated by the administration of adrenalin.[154]

The Antidiuretic Action of Posterior Pituitary Extract.—Whole posterior pituitary extract or pitressin administered parenterally or through nasal insufflation prevents diuresis in patients with diabetes insipidus and in normal individuals who have ingested considerable quantities of fluid. This antidiuretic effect is due to the direct action of the active fraction on the kidney. It causes the reabsorption of water in the thin portion of the loop of Henle and the terminal portion of the proximal convoluted tubule. The effect of this principle is not influenced either by denervation of the kidney or by changes in the blood flow through this organ.[97]

Interestingly enough, posterior pituitary extract also exercises a diuretic effect. This latter action, however, is transient and can be elicited only under special circumstances. Thus, it is best observed in anesthetized animals following rapid intravenous infusion of isotonic glucose or after the administration of phlorizin.[159] This diuretic effect may be due to the pressor rather than the antidiuretic principle.[155]

The presence of an antidiuretic principle of the posterior pituitary raises the very interesting problem concerning the relationship of the pituitary gland to water exchange. In a most illuminating paper which appeared in the Proceedings of the Association for Research in Nervous and Mental Disease in 1936, Richter[156] summarized the results of his experimental studies dealing with this problem. Working with rats, this investigator found that experimental diabetes insipidus could be produced by total hypophysectomy, by section of the stalk as close to the brain as possible without producing brain injury, and by the surgical removal of the posterior lobe of the pituitary. With all of these methods the antidiuretic principle of the posterior lobe is effectively removed from the body economy. However, the *permanence* of the symptoms is dependent on two factors, on (1) the presence of the anterior lobe of the hypophysis and (2) the absence of any brain injury. Where the anterior hypophysis has been surgically destroyed or removed, or when injury to the brain has occurred, diabetes insipidus either is not manifested or is transient in character despite the concomitant removal of the posterior lobe or section of the stalk. This relationship of the anterior pituitary lobe to diabetes insipidus was originally suggested by Von Hann[157] on the basis of clinical and pathological studies in patients with diabetes insipidus, and has been amply confirmed by Richter[156] and by Pencharz, Hopper and Rynearson.[158]

The fact that permanent diabetes insipidus can occur only with the re-

moval of the posterior lobe or by section of the stalk close to the brain in the presence of an intact anterior lobe has caused speculation concerning the presence in the anterior hypophysis of a diuretic hormone capable of balancing the effect of the antidiuretic principle of the posterior lobe The studies of Richter[186] would indicate that no such principle is elaborated by the anterior lobe Rather the disappearance of diabetes insipidus following removal of the anterior lobe or injury to the brain is explained on the basis of the marked reduction in general metabolic activity following such procedures The decrease in water intake following total hypophysectomy was regarded as part of the same phenomenon as the marked reduction in appetite and food intake This observation concerning the mode of action of the anterior lobe on water exchange is endorsed by Rawson Fisher and Ingram [189]

The work of Richter[186] further showed that the primary effect following removal of the hormone of the posterior lobe is polyuria The marked thirst and increased water intake which occurs in diabetes insipidus are secondary responses Thus removal of the posterior lobe results in a marked diuresis which in turn is followed by dehydration increased thirst and increased water intake Ligation of both ureters in the experimental animals studied resulted in a prompt reduction of water intake to fairly normal levels

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Chapter 3

DISEASES OF THE HYPOPHYSIS

I Tumors of the Anterior Lobe of the Hypophysis

In general the manifestations of hypophyseal disease are dependent on whether the underlying pathologic process produces increased hypophyseal activity or causes a reduction in such function The former obtains where there is either an increase in the mass of hormonal secreting cells or where such cells even if not increased in number or size are stimulated to increased activity The latter manifestations occur where the active cells are destroyed through mechanical pressure hemorrhage infarction infection or nonspecific atrophy Not infrequently, a moderate decrease or increase in hypophyseal function may occur in the absence of any overt histologic changes in the cells The simultaneous presence of evidences of hyperfunction and hypofunction of the hypophysis is occasionally observed Such a syndrome is generally due to the presence of so called mixed tumors of the hypophysis[1] but may even be due to a single type cell tumor which produces atrophy of one group of cells and irritative stimulation of another

The clinical manifestations of hypopituitarism vary considerably depending upon the degree of destruction of the hormone secreting cells the age at which such destruction occurs and the sex of the individual Simmonds cachexia represents the classic clinical example of hypopituitarism due to complete or almost complete anterior hypophyseal destruction But considerably more common are those instances of mild or moderate anterior pituitary hypofunction characterized by somatic or genital abnormalties but consistent with a perfectly normal life span In such patients the integrity of vital organs like the adrenals is not seriously threatened since the hypophyseal cells are still capable of secreting adequate if somewhat reduced amounts of adrenocorticotropic factor Actually in such instances there occurs a dissociation of anterior hypophyseal function in which suppression of some hormonal factors occurs with relatively normal secretion of others

The manifestations of anterior hypophyseal hyperfunction are dependent upon which cells are involved in the hypersecretory process Thus a tumor of the eosinophilic cells may produce gigantism or acromegaly while a basophilic cell tumor may be associated with the clinical evidences of Cushing's syndrome In the former instance the evidence of hyperfunction is primarily that of somatic overgrowth while in the latter the hypersecretory effect is due mainly to the overproduction of the factor stimulating the adrenal gland Hyperfunction of the anterior hypophysis therefore is a relatively selective overfunction in which a specific hormone fraction is predominantly produced in increased amounts

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phil cells are generally too small to produce mechanical symptoms It is important to remember however that the size of the mass of hormone secreting cells bears very little relationship to the endocrine abnormalities which it may produce Occasionally extensive calcareous deposits may occur in these tumors in which event they are referred to as adenoma psammosum

CHROMOPHOBE ADENOMAS OF THE ANTERIOR LOBE OF THE HYPOPHYSIS

These are the most common tumors of the pituitary gland and constitute approximately three fourths of the new growths of this gland These tumors originate in the chromophobe cells of the anterior lobe of the hypophysis Since these cells are the parent cells of the basophils and eosinophils but are themselves non secretory in character their endocrine effects are produced as a result of pressure on the contiguous actively functioning hypophyseal or hypothalamic tissue The clinical manifestations are dependent upon the size of the tumor, the age and the sex of the patient They are generally very slow growing tumors and may be present for many years before symptoms of sufficient severity point to the correct diagnosis In a group of 18 patients studied at the Mount Sinai Hospital 10 had symptoms for five years or longer before any definite treatment was instituted Six of this group of 10 patients had symptoms for from seven to fourteen years

The greatest incidence of this disease occurs during the fourth and fifth decades This is in part explained by the fact that symptoms may be present for a number of years before they force themselves seriously upon the attention of the patient and his physician Actually no age is really exempt and the distribution is equal between males and females Of our group of 18 patients 12 cases were between the ages of thirty-one and fifty and the extremes were 1 patient of nineteen and another of seventy years of age These results are identical with a much larger series reported by German[7] and compiled from Cushing s series in the Brain Tumor Registry at Yale Medical School

Symptoms —The symptoms produced by chromophobe tumors are generally a combination of endocrine symptoms which are usually but not always hypopituitary in character and signs of increased intracranial pressure with involvement of the optic chiasm Almost all of our patients complained of symptoms or showed signs attributable to the mechanical presence of an intracranial mass Only rarely were the endocrine manifestations predominant although almost all patients showed some of the latter manifestations to a varying degree

Most patients manifested visual disturbances characterized by failure to see out of the lateral half of each eye and frequently blurring of vision A general loss of visual acuity was a common complaint Objectively bitemporal hemianopsia occurred in over 80 per cent of the patients, and unilateral or bilateral optic atrophy in approximately 50 per cent Over half the patients showed pupillary irregularities such as difference in size of the two pupils with diminished reaction to either light or accommoda

Adenomas of the anterior lobe of the hypophysis are the most common of all intracranial tumors constituting 17 8 per cent of such neoplasms The next most common are craniopharyngiomas, which make up 4 3 per cent [3] If we include small adenomas which produce no symptoms the actual incidence of such anterior hypophyseal growths is considerably greater Among 1,000 unselected cases Costello[4] encountered various sized adenomas of the hypophysis in 25 per cent The greatest incidence occurred in persons in the sixth decade and they occurred with equal frequency in males and females This situation is essentially similar to that which prevails in various other organs Small and at the moment, clinically unimportant adenomas are encountered in one-third of the adrenals of patients who come to postmortem examination

The pituitary may be the seat of various kinds of tumors either benign or malignant, primary or metastatic In addition to the ones which arise *from the cells of the anterior lobe and the craniopharyngiomas*, Kraus[5] lists 11 other types most of which are rather rare Tumors such as the hemangiomas of the anterior lobe lipomas of the posterior lobe hypophyseal chordomas primary sarcomas of the hypophysis infundibulomas, gliomas and ganglioneuromas of the posterior lobe teratomas and true cysts are exceedingly uncommon As a matter of fact tumors of the neural lobe are so rare as to raise a question as to the existence of such primary new growths

TABLE 3 —TUMORS OF THE HYPOPHYSIS (ACCORDING TO KRAUS)

1 Chromophobic eosinophilic and basophilic adenomas of the anterior lobe of the hypophysis
2 Craniopharyngiomas
3 Fibroma of the hypophysis and of the hypophyseal stalk
4 *Hemangioma of the anterior lobe of the hypophysis*
5 Lipoma of the posterior lobe
6 Hypophyseal chordoma
7 Sarcoma of the hypophysis
8 Infundibuloma (Globus[6])
9 Glioma and ganglioneuroma of the posterior lobe
10 Teratoma of the hypophysis
11 Cholesteotoma—usually arising from the infundibular region
12 *True cysts of the hypophysis*
13 Metastatic carcinoma and sarcoma

Tumors of the pituitary may produce symptoms of increased intracranial pressure visual disturbances or endocrine abnormalities Generally the clinical picture presents a combination of all three but with either the endocrine or the mechanical manifestations predominant Where active secretory cells are involved *either directly or indirectly* by the tumor process endocrinologic manifestations will occur Tumors of the eosinophilic or basophilic cells of the anterior lobe of the hypophysis will produce endocrinologic symptoms due to the fact that these cells are active hormone secreting cells Tumors of the chromophobe cells which are non-secretory cells may or may not produce endocrine symptoms depending on the size of the tumor and its mechanical effect on the remainder of the anterior hypophysis and the hypothalamus *Tumors of the baso-*

amic involvement. Similarly, polyuria and polydipsia, although only rarely present, are evidences of pressure on the hypothalamus.

The symptoms enumerated above are those generally seen in adults. The occurrence of such a tumor in childhood may produce pituitary dwarfism. In very young adults the picture of infantilism, the so-called Lorraine-Levi syndrome, may ensue.

The basal metabolic rate is generally lowered. In 60 per cent of the patients observed in our group, the basal metabolic rate varied from −16 per cent to −35 per cent. Of the series reported by German[7] 54 per cent of the patients had basal metabolic rates which were less than −16 per cent. Approximately two-thirds of the patients of our series had normal glucose tolerance curves after the administration of 1.75 grams of glucose per kilogram of body weight. Only 15 per cent showed a rather flat curve, while 25 per cent showed some decrease in glucose tolerance. In only one instance in our group was the latter marked. Anemia is as a rule not present. The white blood cell count and the differential study are normal but with a slight tendency to lymphocytosis.

TABLE 5.—ENDOCRINE SYMPTOMS OF CHROMOPHOBE ADENOMAS IN 100 CASES
CUSHING'S SERIES FROM THE BRAIN TUMOR REGISTRY OF YALE
(Quoted by German[7])

	per cent	
Disturbance in menstrual cycle	97	(females)
Subnormal basal metabolic rate (below −5%)	76	
Fine dry skin	56	
Scanty hair, fine in character, abnormal distribution	53	
Gain in weight	47	
Diminished libido	39	
Subnormal blood pressure	[illegible]	
Diminished potentia sexualis	28	(males)
Subnormal temperature	23	
Somnolence	22	
Genital hypoplasia	15	
Polydipsia (slight)	12	
Mammary hypoplasia	11	(females)
Questionable enlargement of acral parts	9	
Weakness	9	
Polyuria (slight)	9	
Feminine habitus in males	8	(males)
Small acral parts	5	
Appetence for sweets (slight)	5	
Small stature	3	
Glycosuria (slight)	2	

The clinical symptoms and signs discussed above are those which are generally observed to varying degrees in patients with chromophobe adenomas. Occasionally, however, these patients will present symptoms of hyperpituitarism of the acidophilic or basophilic type along with the symptoms of hypopituitarism. Such manifestations occurred in 3 of our patients: 2 with evidences of acromegaly and hypopituitarism in which a chromophobe adenoma was found at autopsy, and 1 patient with many evidences of virilism and Cushing's syndrome in which a chromophobe adenoma was

tion Headache occurred in a third of the instances and when present was generally occipital fronto-occipital or generalized The headaches were never particularly severe although rather persistent and eventually frequently recurring There was occasional nausea but no projectile vomiting The sense of smell was impaired or lost in approximately 25 per cent of the patients

On *x*-ray examination of the skull all patients showed enlargement of the sella turcica generally with some evidence of thinning or destruction of the posterior clinoid process and the dorsum sella The absence of an enlarged sella turcica is a point strongly against the diagnosis of a chromophobe adenoma of significant enough size to produce clinical symptoms

Some abnormality in the spinal fluid examination occurs in approximately two-thirds of the cases The most common finding is an increase in the spinal fluid protein above 40 mgm per cent An increase in spinal fluid pressure above 200 mm of water occurred in only 15 per cent of our patients The colloidal gold curve is generally negative and as a rule there is no increase in the spinal fluid cell count The spinal fluid sugar is frequently slightly elevated

In summary then the non-endocrine symptoms were essentially those of any pituitary neoplasm These symptoms and signs in order of frequency of occurrence were

1 Enlargement of the sella turcica with destruction of the posterior clinoid processes
2 Visual disturbances
   a) Loss of visual acuity blurring of vision occasional diplopia
   b) Bitemporal hemianopsia with constriction of visual fields
   c) Pupillary irregularities
   d) Unilateral or bilateral optic atrophy
3 Abnormalities in the spinal fluid
   a) Increase in total protein
   b) Slight increase in sugar
   c) Occasional increase in spinal fluid pressure
4 Headaches
5 Impairment or loss of olfactory sense
6 Episodes of nausea

The endocrine symptoms are dependent upon the pressure of the tumor on the remainder of the hypophysis and the hypothalamus Most of the symptoms are those of hypopituitarism although occasionally evidence of acidophilic and basophilic hyperpituitarism are observed Generally the endocrine symptoms are not particularly pronounced but occasionally they constitute the predominant aspect of the clinical picture The evidences of hypopituitarism usually observed are amenorrhea or oligomenorrhea loss of libido decrease in hirsutism weight loss asthenia anorexia decrease in size of the genitalia in males and lowered basal metabolic rate The patients often develop a curious pallor referred to as alabaster in character The skin may become rather dry and of a delicate texture the hair scanty fine with change in distribution Weight gain is not infrequently observed and when present is probably evidence of hypothal

flat and rarely a diabetic pattern The peripheral blood count may show a mild lymphocytosis

Pathology and Histology of Chromophobe Adenomas —The chromophobe adenomas are distinguished from tumors of the other pituitary elements on the basis of the staining reactions of the cytoplasmic granules The eosinophilic tumors are those in which the cells when stained with hematoxylin-eosin are seen to contain large eosin staining granules while tumors made up of chromophobe cells contain fine very sparse poorly staining granules The basophilic cells contain large dark abundant basophilic granules The chromophobe tumors are generally benign but malignant chromophobe tumors are encountered Two such cases were observed in our group of patients The malignant tumors produce extensive local invasion but do not tend to metastasize and are therefore occasionally referred to as malignant adenomas'[11]

The benign tumors are usually surrounded by a rather thick capsule over which moderate sized blood vessels may course The mass itself is usually highly vascular and often semi solid in consistency It is generally made up of markedly cellular material and numerous hemorrhages The cell nuclei are oval and frequently contain darkly staining irregularly distributed chromatin material The cytoplasm is generally poorly stained not well demarcated and is either entirely free from granules or contains occasional fine ones In some portions of the tumor the cells may be closely packed and irregularly distributed showing no definite arrangement while in others there is a well-defined alveolar pattern Frequently the cord like arrangements of cells are separated from one another by thin walled blood sinuses

The effect of chromophobe adenomas on the histology of the other endocrine glands is not well defined in great part because so few postmortem studies are available From the data reported in the literature[7] it would seem that the *thyroid* is frequently normal but just as often it is small and atrophied In several cases extensive fibrosis was noted In those instances in which the gland was normal colloid was abundant The *adrenals* are described as being small in 5 of 8 cases examined and normal in 3 The *thymus* is usually small or absent but in 2 instances was quite large The *testes* generally show considerable atrophy with reduction in spermatozoa and, frequently disappearance of the interstitial cells The pancreas was reported as normal in 7 of 9 cases In 1 of the remaining cases there was a slight diffuse fibrosis which also involved the islands of Langerhans while in the other instance some of the islands were described as enormous

Treatment of Chromophobe Adenomas —The methods of therapy available are (1) Surgical removal of the tumor (2) *x* ray treatment or (3) a combination of both Surgery generally consists of incising the capsule of the tumor and evacuating its contents with curette and suction The operative mortality is approximately 10 per cent[12] although Cushing reported a series of 260 patients with an operative mortality of 5 per cent[13] Because of the difficulties attendant upon the removal of the tumor in its entirety the incidence of recurrence after operation is quite high More than 40 per cent of the patients in Cushing s series developed recurrences within

found at operation Twenty two such patients with mild acromegaly and symptoms of hypopituitarism were described by Dott and Bailey[1] and by Bailey and Cushing These authors referred to such cases as instances of mixed adenomas producing a ' fugitive acromegaly The patients presented some of the features of acromegaly such as coarsening of the features enlargement of the hands and feet, excessive height, tufting or squaring of the phalanges, slight increase in the basal metabolic rate hypertrichosis normal or exaggerated libido excessive perspiration and persistent lactation In addition, these patients also had symptoms of *hypopituitarism* Actually as early as 1910 Cushing during a Harvey lecture[10] pointed out that many patients with hypopituitarism showed at least a tendency to hyperpituitarism

The acromegalic symptoms in Bailey and Cushing s series were very slight, while the symptoms of hypopituitarism were predominant In fact the cases were originally classified as typical instances of chromophobe adenomas until the rather subtle evidences of acromegaly were noted The microscopic picture of the tumor in some of these patients was characterized by relatively scant evidence of acidophilic cellular activity fine alpha granules usually appearing as a ring in the peripheral cytoplasm Bailey and Cushing suggested that growths producing the combined picture represent specific mixed adenomas in which the alpha cells remain embryonic in type Careful histologic study of the tumor material of our 3 patients failed to reveal any evidence of a mixed tumor the cells being typically chromophobic Under such circumstances it is possible that the hyperpituitary symptoms may have resulted from the irritative pressure of the tumor on the adjacent cells originally stimulating them to increased secretion and only subsequently producing atrophy

Summary of the Clinical Picture of Chromophobe Adenomas —These tumors produce two groups of symptoms (1) Those associated with the mechanical effects of an intracranial mass and (2) endocrine symptoms due to pressure of the tumor on actively hormone secreting cells In the first group are visual disturbances constriction of visual fields with bitemporal hemianopsia pupillary irregularities unilateral or bilateral optic atrophy headaches and occasional nausea The endocrine symptoms include disturbances in menses in women generally amenorrhea the development of a fine dry skin, a loss of hirsutes in males with a tendency to feminine distribution, loss of libido asthenia anorexia and often either a weight loss or a weight gain Polyuria and polydypsia only rarely occur Occasionally patients develop evidences of hyperpituitarism

Either the mechanical or the endocrine symptoms may be most prominent Generally the former is the case but some endocrine abnormalities are always present to a lesser or greater degree

The roentgen examination of the skull always reveals enlargement of the sella turcica and frequently destruction of the posterior clinoids The spinal fluid examination generally shows some elevation in total protein Only rarely is the spinal fluid pressure increased In more than half the patients the basal metabolic rate is lowered to less than −15 per cent The glucose tolerance curve is usually normal but may sometimes assume a

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a five-year period. In a series of cases reported by Henderson[11] 50 per cent developed postoperative recurrences. These results are very discouraging, but they are considerably improved if the operation is followed by a course of *x*-ray therapy to the pituitary. The incidence of recurrence in such patients subjected to combined therapy was reported to be less than half of that where surgery alone was employed. With *x*-ray treatment alone some improvement in the clinical picture occurs in perhaps a third to a half of the patients. The results in our experience with a dozen patients who received extensive *x*-ray treatment were rather discouraging. These patients had been followed for a period of one to eight years after conclusion of the therapy, and over half had received more than one course. The symptom that was satisfactorily alleviated was the headache, but improvement in vision and enlargement of the visual fields occurred only rarely. In no instance was there any change in the *x*-ray findings in the skull, and the endocrine symptoms, if they were improved at all, were only slightly so. However, the further progress of the disease seemed to be arrested in more than half the patients.

The results in general leave a good deal to be desired, and by far and large the best results are obtained with surgery followed by *x*-ray irradiation. With neither method of therapy does there generally occur any very striking improvement in the hypopituitary manifestations. The visual symptoms may improve considerably provided optic atrophy has not ensued prior to treatment. The visual fields may enlarge and the hemianopsia disappear only if the optic pathways have not been irreversibly damaged by the tumor. The headaches usually respond very satisfactorily to either method of therapy. The choice of treatment is determined primarily by the severity of the mechanical symptoms. If there is a rapidly progressive deterioration of vision with evidence of increasing encroachment on the optic pathways, then immediate surgery should be decided upon followed by *x*-ray treatment. Severe headache with symptoms of an expanding intracranial mass which does not respond to adequate *x*-ray therapy constitutes an indication for surgical intervention. Where the clinical picture is predominantly one of hypopituitarism with relatively little evidence of visual disturbances, *x*-ray irradiation of the pituitary should be the treatment of choice. Patients in whom there occurs a progression of symptoms in general which do not respond despite adequate irradiation therapy should be considered as candidates for surgical intervention. It is well to bear in mind that eight to twelve weeks may elapse after the termination of *x*-ray treatment before definite improvement is noted.

To summarize the indications for therapy, we may say that where the symptoms are relatively mild, *x*-ray irradiation of the pituitary is the preferred treatment. Essentially the same is true where the predominant manifestations are those of hypopituitarism with very little evidence of visual disturbances. Persistent severe headaches and continued progression of the symptoms in general after ample time has elapsed following completion of adequate *x*-ray treatment constitutes a reason for surgical intervention. The rapid progression of visual failure, marked and progressive restriction of the visual fields, and developing pallor of the optic discs call for prompt surgical removal of the tumor to be followed by a course of *x*-ray treatment.

Often the most that can be hoped for is to arrest the progress of the disease and prevent further deterioration

Whatever hypopituitary manifestations remain after adequate time has elapsed following x ray or surgical treatment can be alleviated to some degree by suitable replacement therapy Small doses of dessicated thyroid extract will improve although not entirely control the symptoms associated with a lowered basal metabolic rate Where gonadal atrophy is marked in the male testosterone should be administered This is most effectively done by pellet implantation It is important to remember however that no substitution therapy should be attempted until enough time has elapsed to permit maximum restoration of function of the pituitary and the other endocrine glands following the x ray or surgical therapy

Illustrative Cases

CASE 1 —The patient was a male forty years of age who complained of recurrent frontal headaches of five years duration During the past year the headaches had increased both in frequency and intensity and tended to last for many hours During the past year too the patient had noticed a progressive impairment of vision with some blurring His memory had become poor His sexual desires had gradually decreased during the course of the past five years and erections and orgasms occurred with a progressively diminishing frequency Hirsutism all over the body had become somewhat scant and facial hirsutism had become so slight as to require having only at weekly intervals He had gained 25 pounds in weight over the past ten years There had been no polydypsia or polyuria On physical examination the patient presented a eunuchoid habitus The shoulders were narrow and the hips rather wide with girdle obesity He weighed 78 2 kilos (178 pounds) The skin was smooth and delicate and there was very little hair on his face chest or in the axillae The pubic hair was scanty and feminine in distribution The penis was rather small but the testes appeared quite normal There was considerable restriction of the visual fields with a bitemporal hemianopsia The left disc appeared slightly pale The x ray examination of the skull revealed a marked enlargement of the sella turcica with partial erosion of the posterior clinoid processes The basal metabolic rate was plus 4 per cent and the blood pressure was 110 80 mm of mercury The peripheral blood count showed a hemoglobin of 91 per cent 4 5 million red blood cells per cmm and 7 900 white blood cells The differential smear revealed 70 per cent polymorphonuclear leucocytes and 30 per cent lymphocytes The glucose tolerance curve after the administration of 1 75 grams of glucose per kilogram of body weight was as follows

	mgm per cent
Fasting blood sugar level	80
After ½ hour	110
1	170
2 hours	145
3	135

Examination of the spinal fluid revealed a pressure of 80 mm of water There were no white blood cells a one plus pandy and negative colloidal gold and Wassermann tests The spinal fluid protein was 60 mgm per cent

Because of the severity and progression of the visual symptoms it was decided to operate upon this patient Upon operation a solid and rather bloody tumor was found which was not well demarcated from the surrounding cerebral tissues A considerable part of the tumor was removed by curetting and suction Microscopic examination of the tumor showed it to possess unusual

vascularity Large areas of frank hemorrhage were observed in the section The tumor cells appeared fairly uniform in size and possessed round vesicular nuclei with dark staining chromatin granules Many of them seemed to possess a nucleolus The cytoplasm was moderate in amount and with hemotoxylin-eosin stained a diffuse bluish color No granules were observed in the cytoplasm A number of alveolar structures distended with a diffuse pink staining colloid material were seen to occupy scattered areas The histological diagnosis was chromophobe adenoma

Following operation the patient received two extensive courses of x ray therapy extending over a five-month period He was then followed during fairly frequent intervals for the next nine years At his final discharge from the hospital nine years after the operation his visual fields had remained unaltered, although his visual acuity had improved somewhat and the blurring had entirely subsided The headaches had disappeared shortly after the operation His general condition was excellent but no improvement had occurred in the hypopituitary manifestations His general physical habitus was unaltered there had occurred no increase in hirsutism and no improvement in libido X ray examination of the skull showed no change from that seen prior to the operation

Comment —This is a fairly typical clinical picture of chromophobe adenoma, with the usual combination of mechanical and endocrine symptoms The tumor however was less well encapsulated than is generally the case It is important to note the marked degree of vascularity of the tumor and the presence of hemorrhage This is common and in many instances plays an important role in the sudden accentuation of the symptoms and sometimes their spontaneous subsidence

CASE 2 —The patient was a male fifty three years of age who had had symptoms for approximately eight years prior to admission to the hospital His early symptoms were characterized by episodes of drowsiness and somnolence which would come on suddenly every few week and last for two or three days During these periods of somnolence he could be aroused but his speech was thick and confused Beginning with this early period he noticed pain and progressively diminishing vision in the left eye During the course of the next two years the left eye began to bulge and the left eyelid to droop There followed impairment of memory diminution in libido and one year before admission to the hospital severe headaches involving the entire head polydipsia and polyuria and a weight gain of 10 pounds Shortly before admission to the hospital he developed recurrent episodes of fever which lasted for several days and then subsided spontaneously The fever would reach a height of 103 F

On physical examination the patient was found to be a short very obese individual weighing 80 kilograms (176 pounds) His skin was soft and delicate with scanty facial axillary and pubic hirsutism The genitalia appeared quite normal to gross examination The prostate was adequate in size and consistency The left pupil was larger than the right and reacted poorly to both light and accommodation The left eye bulged considerably with a droop of the left upper lid The left fundus appeared quite pale but there was constriction of the visual fields of both eyes with a bitemporal hemianopsia The blood pressure was 140/100 mm of mercury

The laboratory data was as follows The hemoglobin red blood count white blood count, and differential were perfectly normal The basal metabolic rate was -14 per cent The glucose tolerance curve revealed a markedly diminished glucose tolerance Employing 1 75 grams of glucose per kilogram of body weight the blood sugar curve was as follows

	mgm per cent
Fasting blood sugar level	85
After ½ hour	125
1	160
2 hours	180
3	175

The lumbar puncture showed the spinal fluid to be under increased pressure the pressure measuring 320 mm of water The Pandy was strongly positive and the spinal fluid protein was increased to 128 mgm per cent The cell count was normal and the colloidal gold curve and the Wassermann test were both negative

X ray examination of the skull showed a marked enlargement of the sella turcica with a destructive process involving the floor and dorsum of the sella the sphenoid sinus left optic foramen and left lesser wing of the sphenoid

It was assumed that the patient had a neoplasm probably a meningioma at the base of the skull extending from the middle fossa into the retro-orbital region He was given intensive *x* ray treatment over the course of the next three months Despite the irradiation therapy the symptoms progressed visual failure and headaches became more marked and the patient was readmitted to the hospital for operation following which he died

At autopsy the tumor was found to be lobulated darkish red in color and of a jelly like consistency It shelled out readily and was smoothly encapsulated on all but its ventral surface The tumor had spread the ventral lobes apart and compressed and thinned the floor of the 3rd ventricle The circle of Willis was displaced to the right and dorsally and the internal carotid arteries were incorporated in the mass The landmarks at the base of the skull especially the sella turcica were obliterated The internal portions of the sphenotemporal bones on the left side were fragile and appeared to be infiltrated with tumor tissue

On microscopic study the tumor tissue stained with hematoxylin and eosin proved to be very cellular and vascular The cells of which the tumor was composed were deeply staining round and cuboidal containing large round vesicular nuclei and abundant cytoplasm The cells were fairly uniform in size and shape and tended to form clumps and streams with a minimum amount of intercellular substance In some places they assumed a follicular arrangement forming a cyst surrounded by several layers of columnar shaped cells The cytoplasm of these cells stained a deep homogenous non granular blue with hematoxylin-eosin No granules were noted in any of the cells when stained by the Mallory method Large extravasations of well preserved blood elements were seen throughout the sections No mitotic figures were noted With the Mallory stain the cells were seen to be chromophobic In many areas fragments of bone and portions of connective tissue resembling dura were seen apparently pocketed by the invading tumor In the region of the internal carotid arteries the tumor tissue was not only in contact with the adventitia of the blood vessel but also enclosed several nerve trunks indicating that the cavernous sinus was invaded by the tumor No posterior lobe tissue was found

The final pathologic diagnosis was malignant chromophobe adenoma of the pituitary body

Comment —The tumor in this case was characterized by marked local invasiveness Clinically it produced both endocrine and mechanical symptoms the former indistinguishable from that observed in benign chromophobe tumors The mechanical symptoms were perhaps more marked than is ordinarily observed in benign tumors in that the *x* ray evidence of

a destructive lesion was greater and the clinical signs of an intracranial expanding mass were more marked The more marked mechanical signs cannot be relied upon entirely to help differentiate clinically between a benign and a malignant chromophobe adenoma When the evidences of a rapidly progressive expanding and destructive intracranial lesion are present the diagnosis of a malignant adenoma must be suspected But such exaggerated signs are not always present In the other pathologically proven malignant chromophobe case in our group the clinical picture was indistinguishable from that observed in the patients with a benign tumor

It is interesting to note that the illness lasted for over eight years in the patient whose history is recorded above, and of course it is impossible to know whether the tumor was malignant from the very beginning or only became so subsequently That the former is perhaps correct is suggested by the fact that the patient developed bulging of the left eye almost from the very beginning a sign which one would not expect in the presence of a benign chromophobe adenoma Although there is no available data on the frequency with which carcinomatous degeneration of chromophobe tumors occur it has been suggested that such degeneration in eosinophilic adenomas is as high as 20 per cent[15]

Case 3 —The patient is a male forty four years of age who was quite well until eleven months ago when he was suddenly seized with an attack of weakness nausea and malaise while driving his automobile He was taken home and put to bed where he remained for the next four months Any effort to get out of bed was associated with profound asthenia and loss of consciousness which lasted for several minutes During the first two months of his illness the patient had severe anorexia and lost 40 pounds in weight His appetite subsequently improved and he regained 35 pounds Prior to the onset of his illness the patient had been a rather ruddy complexioned person but he has since become pale and his skin has assumed an alabaster appearance He had lost all the hair from his face chest and legs while the scalp pubic and axillary hirsutism remained unaffected but during the course of the past two months there has been a return of hair growth to the affected parts in a rather patchy distribution Two months after the onset of the disease there was a sudden loss of libido and a failure of penile erections and ejaculations which has continued to date Simultaneously with this the patient began to develop hot flashes which have become increasingly more frequent There has occurred a definite decrease in the size of the penis and testes For the past two months the patient has noted recurrent episodes of swelling of the hands and stiffness of the fingers There has occurred no impairment of vision and only occasional frontal headache

On physical examination the patient was a rather well developed person with no abnormal distribution of fat His skin was thin and delicate and had a curious pallor The hair on his head was patchy and thin and the axillary and pubic hair was sparse the latter assuming a female pattern of distribution The penis was small both testes were small and atrophic and the prostate was flat The fundi were perfectly normal and there was no encroachment on the visual fields The basal metabolic rate was -1 per cent and the blood pressure was 84/70 mm of mercury

The x ray examination of the skull showed the sella turcica to be markedly enlarged The floor of the sella was depressed while the dorsum sella was thinned and elongated There was considerable atrophy of the posterior clinoid processes

The red cell count and hemoglobin were normal The white cell count was 3 400 per cmm of which the segmented polymorphonuclear leucocytes tot

alled 50 per cent the non segmented 4 per cent the eosinophils 3 per cent and the lymphocytes 43 per cent The serum sodium was 133 1 meq/l A twenty four urine specimen showed a total absence of neutral 17 ketosteroids An oral glucose tolerance curve was quite flat

	mgm per cent
Control blood sugar	56
½ hour after administration of 1 75 grams of glucose/kilo	70
1 hour after administration of 1 75 grams of glucose/kilo	73
2 hours after administration of 1 75 grams of glucose/kilo	54

The results of an intravenous glucose tolerance test were not very different From a control blood sugar level of 70 mgm per cent a maximum peak of 92 mgm per cent was reached with a maximum drop to 65 mgm per cent

A tracer dose of I^{131} was administered and 65 per cent of the administered dose was excreted in two days a result consistent with either euthyroidism or hypothyroidism

A lumbar puncture showed the spinal fluid to be under normal pressure (140 mm of water) There were 4 cells all of which were lymphocytes the Pandy and the colloidal gold were negative but the spinal fluid protein was increased to 82 mgm per cent

It was decided to treat this patient with x ray therapy and at the time of this writing such therapy had been started

Comment —The picture which this patient presents is predominantly that of hypopituitarism while the mechanical symptoms are negligible and the signs limited to enlargement of the sella turcica and a moderate increase in spinal fluid protein The manifestations of hypopituitarism are particularly reflected in the decrease in size and function of the gonads and evidence of decreased adrenal cortical function The latter is suggested by the marked asthenia the nausea weight loss hypotension flat glucose tolerance curve decrease in the serum sodium level and finally the total absence of the urinary excretion of neutral 17 ketosteroids

It is of great interest that the symptoms of this patient appeared very suddenly and that subsequently many symptoms disappeared or improved spontaneously One can only speculate as to the nature of the mechanism that permits of such a phenomenon The tumor had unquestionably been there for a relatively prolonged period of time since the enlargement and thinning of the sella turcica was quite marked It is possible that the symptoms were ushered in by a sudden hemorrhage into the tumor substance causing a further sudden increase in the size of the tumor and destruction of hormone secreting cells One recalls that these tumors are very vascular and that hemorrhage is not infrequently seen in the tumor substance Some improvement in the symptoms might perhaps be expected with resorption of the blood

The important argument against immediate surgical intervention in this instance was the paucity of mechanical symptoms There was no evidence

of visual disturbance or the development of optic atrophy or reduction of the visual fields In the opinion of most investigators these signs and symptoms constitute the major reason for the surgical removal of the tumor It was consequently felt that the patient should be given *x* ray therapy to the pituitary

CASE 4 —The patient was a thirty nine year old woman whose symptoms dated back to the age of thirty two at which time she suddenly developed amenorrhea which has continued throughout the course of her illness Shortly after the cessation of menses the patient noticed an enlargement of the right side of the neck which increased during the course of the next two years to involve both sides of the neck With this she developed some nervousness, sweating cardiac palpitation weakness and some weight loss One year prior to admission to the hospital that is six years after the onset of the illness the patient noticed that her facial features were becoming considerably coarsened and increased in size Her nose became quite large the lower jaw prominent and the lips and tongue thick and coarse Her hands and feet were much enlarged and the fingers and toes were thick and spade like The hair of her head became streaked with gray the axillary hair disappeared and the pubic hair became scant With the onset of the acromegalic symptoms the patient began to develop daily recurrent headaches behind the right eye brow and a definite diminution of vision of the right eye

On physical examination the patient was a thick set person with definite acromegalic features The nose and jaw were massive the lips and tongue thick the eyebrows overhanging The hands and feet were large and the fingers and toes flat The thyroid was markedly enlarged firm and fairly smooth The skin appeared rather dry The right pupil was larger than the left both reacted slightly to light but well to accommodation The right optic disc was dead white and the left paler than normal Cross vision was considerably impaired in the right eye and there was an external strabismus of that eye There was marked narrowing of the visual fields The blood pressure was 122/70 mm of mercury

The *x* ray examination of the skull showed the sella turcica to be markedly enlarged with erosion and thinning of the dorsum sellæ and the anterior and posterior clinoid processes An *x* ray examination of the chest revealed the presence of a substernal thyroid

The hemoglobin was 56 per cent the red blood cell count 4 35 million per cmm the white blood cell count 5 100 per cmm with 60 per cent segmented polymorphonuclear leucocytes 2 per cent non-segmented forms 34 per cent lymphocytes 2 per cent monocytes 1 per cent basophils and eosinophils each The basal metabolic rate on three different occasions was plus 46 plus 45 and plus 42 per cent The glucose tolerance curve following the oral administration of 1 75 grams of glucose per kilogram of body weight was as follows

	mgm per cent
Fasting blood sugar	85
After ½ hour	190
" 1	140
" 2 hour	85
3	75

The patient was operated upon and the tumor was found to be covered by a thick capsule which was incised and the tumor removed by curetting inside the capsule The patient died three days after the operation

Microscopic examination of the tumor tissue after staining with hematoxylin-eosin revealed closely packed cells arranged in poorly defined cord like and acinar formation Ramifying throughout the tissue were many blood filled

paces The cells were polygonal in shape fairly large and uniform except for an occasional particularly large cell The nuclei were round and vesicular and deeply stained There were many cells with 2 or 3 nuclei The cytoplasm was abundant and stained faintly No granules were seen but many mitotic figures were observed The microscopic diagnosis was chromophobe adenoma of the pituitary

Comment —This case is of considerable interest because it represents an instance of a chromophobe tumor producing both hyper and hypopituitarism The former are reflected in the acromegaly enlargement of the thyroid and increased basal metabolic rate and the latter in the amenorrhea and the reduction in axillary and pubic hirsutism In addition the patient had marked impairment of vision and considerable encroachment on the visual fields The acromegaly was by no means the most florid type but nevertheless so well defined that the stigmata were unmistakable As mentioned previously this combination of the two groups of symptoms occur not too infrequently but the microscopic section of the tumor in this patient failed to reveal any cells which could even remotely be classed as eosinophilic Nevertheless the acromegalic manifestations which this patient presented could only be due to increased activity of acidophilic elements

Case 5 —The patient is a thirty two year old woman who was perfectly well until the age of eighteen when she noticed that her menses were becoming irregular Her periods had begun at the age of thirteen and were perfectly normal for the next five years The irregularity of the menses beginning at the age of eighteen became progressively worse during the next ten years and then she ceased to menstruate entirely With the amenorrhea she noted a gradual increase in weight and at the time of admission to the hospital four years later she was quite obese Seven years prior to admission to the hospital she began to develop hair on the face breasts chest lower back and legs By the time of admission to the hospital the hirsutism had become quite marked During this period hypertension had been noted from time to time Six months before admission to the hospital she began to experience blurring of vision and right parietal headaches which radiated to the right temple and posteriorly to the occiput

On physical examination the patient was quite obese with a thick neck and chest and rather slender upper and lower extremities She had considerable hirsutism of the face breasts back and extremities There were no striae The left pupil was larger than the right and although both reacted to light reaction to accommodation was uncertain Both optic discs showed some pallor and visual field examinations showed marked concentric narrowing The blood pressure was 120/70 mm of mercury and the basal metabolic rate was −20 per cent on one occasion and −9 per cent on another The hemoglobin was 85 per cent the white blood cell count 6 800 of which 63 per cent were segmented polymorphonuclear leukocytes 9 per cent non segmented forms 24 per cent were lymphocytes 4 per cent monocytes and 1 per cent basophils An oral glucose tolerance test following the administration of 1 75 grams of glucose per kilogram of body weight was as follows

	mgm per cent
Control fasting blood sugar	80
After ½ hour	200
After 1	170
2 hours	100
3	130

A lumbar puncture showed the spinal fluid to be under normal pressure Globulin was absent there were 3 cells which were monocytes, and the colloidal gold curve was negative

An x ray examination of the skull revealed the sella turcica to be markedly enlarged, and in addition there was hyperostosis frontalis interna Further x ray examination of the spine and long bones failed to reveal any osteoporosis

Because of progressive increase in the intensity of the headache and a rather rapidly failing vision despite an adequate course of x ray therapy to the pituitary surgical removal of the tumor was decided upon At operation the tumor was found to be a reddish brown mass covered with a tough resistant capsule on the surface of which several fair sized blood vessels coursed The capsule was incised and a moderate amount of dark brown liquid escaped The contents of the cyst were then curetted and pinkish brown tumor tissue removed

On histologic examination the material consisted of fragments of densely *cellular tissue* The *cells* were grouped about *fairly numerous thin walled* vascular channels in a rather uniform organization The dominant cell form was large round or pentagonal in outline containing a large deeply staining nucleus surrounded by abundant cytoplasm The cytoplasm stained deeply red but no granules were seen The histologic diagnosis was chromphobe adenoma

Following the operation the patient was given further x ray therapy to the pituitary A follow up study over a four year period showed no change *in vision visual fields or hirsutism although the headaches had disappeared* entirely

Comment —As in the previous instance this patient presented some evidence of hyperpituitarism Here the symptoms of the hyperpituitarism however were those ordinarily associated with increased activity of the basophilic cells of the anterior hypophysis such as the hirsutism curious obesity decreased glucose tolerance and occasional hypertension The microscopic sections of the tumor however failed to reveal any basophilic cells It is possible that *these symptoms may be hypothalamic in origin* since there is some evidence to indicate that hypothalamic lesions may perhaps produce the clinical picture of Cushing s syndrome [19] In any event both cases cited above emphasize the importance of bearing in mind that chromophobe tumors are capable of producing a combination of hyperpituitary and hypo pituitary manifestation The former may simulate tumors of the hormone secretory cells of the adenohypophysis

THE CRANIOPHARYNGIOMAS

The craniopharyngiomas are the second most frequent type of intra *cranial* tumor after the *chromophobe* adenomas constituting 4 3 per cent of such new growths [3] They are congenital tumors which are derived from rests of squamous epithelium of the hypophyseal duct Such cellular rests are found in three quarters of the adult pituitaries[16] and are usually found on the anterior and superior parts of the anterior lobe of the hypophysis as well as in the pars infundibularis The term craniopharyngioma was originally suggested by Cushing [13] Actually as pointed out by Globus and Gang[17] it is *the upward evagination of the embryonal oral cavity* rather than the pharynx which later becomes the hypophyseal duct and subsequently Rathke s pouch Eventually this upward evagination gives rise to the anterior lobe of the hypophysis while a downward evagination from

the floor of the third ventricle finally forms the posterior lobe In the course of development the hypophyseal duct disappears leaving behind squamous epithelial rests which find their way to the surface of the infundibulum during the rotation of Rathke's pouch When the craniopharyngioma originates in the cell groups dispersed into the anterior lobe of the hypophysis an intrasellar tumor results whereas if it arises from cell rests in the pars infundibularis a suprasellar tumor is formed

These tumors vary considerably in size and may be solid cystic or partially cystic The cysts may be multilocular attain a huge size and are usually filled with a fluid containing cholesterol crystals The fluid may be colorless yellowish brown or reddish brown and may be of a serous or gelatinous character The cystic areas are frequently converted into solid calcified masses which show up in a characteristic fashion on x ray examination of the skull as suprasellar calcifications although calcification may occur in the solid tumors too According to Kraus[5] the craniopharyngiomas may undergo carcinomatous degeneration The cystic tumors are somewhat more common than the solid ones the so-called adamantinoma

The character of the symptoms produced by the craniopharyngiomas is readily understandable if we appreciate the mechanical effects of these growths The intrasellar craniopharyngiomas actually crowd out and compress the hypophysis and produce a widening and thinning of the sella turcica When the tumor lies outside of the sella arising from the pars infundibularis it is then usually within the circle of Willis and behind the optic chiasm The floor of the third ventricle is pushed upward and may be thinned or actually destroyed so that part of the tumor may be in the ventricle[6]

The histology of these tumors is quite variable In general the solid parts are made up of squamous cell rests embedded in a fibrous stroma Degenerative changes with liquefaction may occur and pseudocysts thus form Around these liquefied necrotic areas foreign body giant cell formation and calcification may occur and deposits of hemosiderin and cholesterol crystals take place[5] Sometimes embryonal residues simulating hair follicles sebaceous cells bone and cartilage may be found in the calcified regions[18] In the true cystic craniopharyngiomas the lining of the cysts is made up of 2 or more layers of epithelium of prickle cells Budding from the walls of the cysts are papillary vegetations covered by squamous epithelium the stroma of which may be rich in blood vessels[5]

Symptoms —The craniopharyngiomas occur commonly during childhood and adolescence but are seen with a fair degree of frequency during adult life Thus Frazier and Alpers[20] reported that 70 per cent of their patients with adamantinomata were under twenty years of age Bailey Buchanan and Bucy[1] in an analysis of the age incidence of 138 cases collected from the literature found that 66 were under the age of twenty while the remaining 72 patients varied in age from over twenty to over sixty years Of the 138 patients 20 were less than ten years of age Of the 14 patients observed at the Mount Sinai Hospital and previously reported upon by Globus and Gang[17] 6 varied in age between twenty and fifty four years while 8 were between three and one half and sixteen years of age when they first came under observation at the hospital Actually in one of the two

children who were seen for the first time at the age of three and one half symptoms highly suggestive of an intracranial tumor dated back to the age of 13 months In this respect the craniopharyngiomas differ from the chromophobe adenomas in that by far and large the former tend to appear considerably earlier in life than do the latter Craniopharyngiomas occur with equal frequency in males and females Of our group the incidence was equally divided between the two sexes and this is approximately true of the cases reported in the literature

Cystic tumors occurred in 9 patients and in the remaining 5 the tumors were solid (adamantinoma)[17] The clinical manifestations were not particularly influenced by the cystic or solid character of the growth

These tumors are not made up of hormone secreting cells Consequently the character of the symptoms which develop are dependent upon the mechanical effects which the tumors exercise by virtue of their size and location Their proximity to and compression of the pituitary and hypothalamus result in the production of endocrine symptoms while the frequency with which the optic chiasm, optic tracts, and oculomotor nerves are involved insures the development of visual disturbances In short as with chromophobe adenomas these tumors produce both the evidences of an expanding intracranial lesion and endocrine symptoms The latter manifestations of the craniopharyngiomas are quite similar to those produced by the chromophobe adenomas except that the incidence of hypothalamic symptoms is much greater in the former than in the latter Thus obesity polyuria and polydipsia thermal disturbances and somnolence are not uncommon in craniopharyngiomas In addition they show evidences of hypopituitarism such as hypogonadism infantilism amenorrhea and in older male patients a loss of libido An occasional patient will show mild acromegalic manifestations In these respects the symptoms are similar to those observed in patients with chromophobe tumors Some difference in the endocrine manifestations is due to the fact that craniopharyngiomas so often involve a much younger age group

By far the most outstanding symptoms occurring in craniopharyngiomas are those of increased intracranial pressure Headache occurs very frequently and was observed in every patient reported by Globus and Gang[17] The localization of the headache is not particularly specific nor is it of any undue intensity or duration but it is frequently accompanied by vomiting The visual disturbances are characterized by papilledema optic atrophy visual field defects particularly unilateral or bilateral temporal field involvement diminution in visual acuity diplopia and extrinsic ocular manifestations The latter in one form or another occur in most cases and consist of ptosis of the lids which is usually unilateral paralysis of one or more eye muscles particularly the internal and superior recti and pupillary irregularities Unilateral proptosis occasionally occurs

The x ray examination of the skull generally reveals an enlargement of the sella turcica frequently with erosion of the clinoid processes In addition abnormal calcifications are seen in the suprasellar region in most instances It has been reported that such calcifications are observed in 80 to 90 per cent of the patients although they were noted in only slightly more than half of the group studied at the Mount Sinai Hospital[17] Oc

casionally such calcifications are observed within the sella. When present the suprasellar calcifications are characteristic of craniopharyngiomas. Air injections frequently show dilated lateral ventricles and occasionally a dilatation of the third ventricle.

The spinal fluid is generally normal in this disease. Increase in spinal fluid pressure, or elevation of protein content or increase in the number of cells occurs only rarely.

Summary of the Clinical Findings.—The two major groups of symptoms are the endocrine symptoms and those due to an intracranial mass. The endocrine symptoms are hypothalamic and pituitary in origin. The former include obesity, polyuria and polydipsia, disturbances in temperature regulation and somnolence. The latter are generally hypopituitary in character and include infantilism, hypogonadism, amenorrhea and in the older age group loss of libido. The basal metabolic rate is frequently lowered.

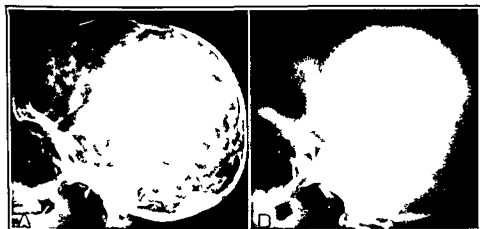


FIG. 3.—*A*, Plain lateral roentgenogram of the skull in a child with a craniopharyngioma showing a normal sized sella without atrophy, except for the truncation of the posterior clinoid processes, increased convolutional markings, separation of the cranial sutures and suprasellar calcification.

B, Laminagram through the midline in the same case showing the suprasellar calcification much more clearly. (Davidoff and Epstein's The Abnormal Pneumoencephalogram.)

Occasionally hyperpituitary manifestations are also present and these are evidenced essentially by a mild acromegaly.

The mechanical symptoms include headache, vomiting, diminution in visual acuity, diplopia and rarely convulsive episodes. Papilledema and optic atrophy occur not infrequently. Visual field defects, particularly involvement of the temporal field either unilaterally or bilaterally, is often observed. This is equally true of extrinsic ocular defects, such as ptosis of one or both lids, paralysis of the various eye muscles, pupillary abnormalities and even occasionally unilateral proptosis.

By far and large the signs of increased intracranial pressure constitute the predominant aspect of the clinical picture although almost all patients will show some endocrine abnormalities.

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Cystic tumors occurred in 9 patients and in the remaining 5 the tumors were solid (adamantinoma).[17] The clinical manifestations were not particularly influenced by the cystic or solid character of the growth.

These tumors are not made up of hormone secreting cells. Consequently, the character of the symptoms which develop are dependent upon the mechanical effects which the tumors exercise by virtue of their size and location. Their proximity to and compression of the pituitary and hypothalamus result in the production of endocrine symptoms, while the frequency with which the optic chiasm, optic tracts and oculomotor nerves are involved insures the development of visual disturbances. In short, as with chromophobe adenomas these tumors produce both the evidences of an expanding intracranial lesion and endocrine symptoms. The latter manifestations of the craniopharyngiomas are quite similar to those produced by the chromophobe adenomas except that the incidence of hypothalamic symptoms is much greater in the former than in the latter. Thus obesity, polyuria and polydipsia, thermal disturbances and somnolence are not uncommon in craniopharyngiomas. In addition they show evidences of hypopituitarism such as hypogonadism, infantilism, amenorrhea and in older male patients a loss of libido. An occasional patient will show mild acromegalic manifestations. In these respects the symptoms are similar to those observed in patients with chromophobe tumors. Some difference in the endocrine manifestations is due to the fact that craniopharyngiomas so often involve a much younger age group.

By far the most outstanding symptoms occurring in craniopharyngiomas are those of increased intracranial pressure. Headache occurs very frequently and was observed in every patient reported by Globus and Gang.[17] The localization of the headache is not particularly specific nor is it of any undue intensity or duration but it is frequently accompanied by vomiting. The visual disturbances are characterized by papilledema, optic atrophy, visual field defects, particularly unilateral or bilateral temporal field involvement, diminution in visual acuity, diplopia and extrinsic ocular manifestations. The latter in one form or another occur in most cases and consist of ptosis of the lids, which is usually unilateral, paralysis of one or more eye muscles, particularly the internal and superior recti, and pupillary irregularities. Unilateral proptosis occasionally occurs.

The x-ray examination of the skull generally reveals an enlargement of the sella turcica, frequently with erosion of the clinoid processes. In addition, abnormal calcifications are seen in the suprasellar region in most instances. It has been reported that such calcifications are observed in 80 to 90 per cent of the patients,[2] although they were noted in only slightly more than half of the group studied at the Mount Sinai Hospital.[17] Oc

hood of any marked endocrinologic reversals except in very young people is unlikely

Illustrative Cases

CASE 1 —The patient was a young woman of twenty five who had been quite well until the age of twenty at which time her menses suddenly ceased During the next several years she developed severe anorexia marked weakness polyuria and marked parieto-occipital headaches She lost approximately 20 pounds in weight For two years prior to admission to the hospital she noticed a progressive decrease in visual acuity recurrent episodes of vertigo and loss of pubic and axillary hair One year before admission to the hospital she began to vomit The vomiting increased in frequency and was projectile in character

On physical examination the patient was found to be a thin rather small person with scanty pubic and axillary hair The uterus and adnexa were infantile in character There was a marked diminution in visual acuity bitemporal hemianopsia and bilateral optic atrophy with papilledema The pupils were unequal in size There was a left internal rectus weakness and a right central facial asymmetry The blood pressure was 100 mm of mercury systolic and 84 diastolic The patient was somewhat anemic the hemoglobin being 65 per cent and the red blood cell count 3 7 million per cmm The white blood count was 6 400 per cmm with some increase in lymphocytes The basal metabolic rate was −10 per cent An *x* ray examination of the skull revealed a markedly enlarged sella turcica with erosion of the posterior clinoid processes and areas of irregular calcifications in the suprasellar region

The patient was treated with *x* rays to the pituitary region which was continued daily for a three-week period At the end of this time there occurred some improvement in visual acuity with widening of the visual fields The improvement continued during the course of the next several months with some subsidence of the headache and vomiting and a diminution of the polydipsia and polyuria She gained 15 pounds in weight there was perhaps some increase in pubic hair and on one occasion she had a fairly normal menstrual period The improvement was unfortunately short lived and after several months the headache returned and became progressively more intense Visual acuity diminished and the restriction of the visual fields became more marked

Approximately one year after completion of *x* ray therapy the patient was subjected to a transfrontal craniotomy A cystic tumor a craniopharyngioma was found in the region of the optic chiasm Its contents were emptied and as much of the capsule as could be safely removed was excised Directly after the operation the patient developed an irregular fever which attained levels of 103 F but was associated with a disproportionately slow pulse The fever continued for approximately three weeks and then began to subside and with its subsidence there occurred some betterment in the clinical condition as was evidenced by a gain in weight and an increase in vision The improvement lasted for only one month and was followed by further impairment in vision marked vomiting and intense headache The patient became disoriented and she developed ptosis of the right eyelid paralysis of the right internal rectus muscle left facial weakness and a bilateral Babinski She became progressively more lethargic lapsed into coma and died approximately two months after the operation

On autopsy an organized discolored mass was found at the base of the brain in the region of the pituitary which involved the optic chiasm and nerves However no recognizable hypophyseal tissue could be found Histologic sections of the mass stained with hemotoxylin and eosin revealed collections of epithelial cells with acinar formation Within this region were numerous calcified bodies hyalinized epithelial cells and multinucleated giant cells

Comment — There are several things of interest to note about this case The relatively long duration of the illness which in this instance lasted

It is perhaps worth mentioning that various neurological abnormalities are sometimes observed in patients with craniopharyngiomas. Thus pyramidal tract signs such as a positive Babinski or Hoffmann sign, absent abdominal reflexes, and variations in the strength of deep tendon reflexes are not infrequently observed. Globus and Gang[1] have described the presence of cerebellar signs including generalized hypotonia, tremor and unsteady gait, and more than half the patients described by these authors manifested evidence of unilateral central facial weakness. However, the neurological findings just described are rarely pronounced and are generally elicited only if carefully looked for.

The x-ray examination of the skull will usually show enlargement of the sella turcica, perhaps some destruction of the clinoid processes, and generally suprasellar calcifications. The latter are almost pathognomonic of craniopharyngiomas. Air injections might reveal dilation of the lateral ventricles and, more rarely, that of the third ventricle.

The peripheral blood count is generally normal, and the spinal fluid is usually negative. Only rarely does there occur an increase in spinal fluid pressure or an increase in the protein content or number of cells.

Treatment of Craniopharyngiomas.—The methods of treatment available at the present time are deep x-ray therapy and surgical intervention. The results of x-ray therapy are unsatisfactory. An occasional patient will show a temporary remission of symptoms with expansion of the visual fields such as occurred in one of our cases. Most patients will fail to show any response to this form of treatment.

The results of operative intervention are by no means satisfactory. Adequate operative procedures are associated with a formidable immediate and delayed postoperative mortality. The latter is generally preceded by a marked hyperthermia.

The ideal surgical treatment of this condition involves the evacuation of the cystic contents of the tumor and removal of the cyst wall. Where the surgical procedure is limited to evacuation of the cyst contents alone, the operative mortality rate is relatively low, but the improvement in symptoms is comparatively slight and of relatively short duration. This is in part due to the rapid reaccumulation of the contents of the evacuated cysts, and in part to the multilocular cystic character of the tumor. The attempts at extensive removal of the cyst walls in order to induce a cure is promptly followed by a considerable increase in the mortality rate. In general, the total removal of the tumor surgically would appear to be a difficult feat and unlikely of achievement. Cushing[13] has emphasized that the reduction in the mortality rate would depend upon the development of techniques which will permit of the destruction of the multilocular cysts *in situ*.

It should be stressed that the indications for surgical intervention in craniopharyngiomas are the mechanical evidences of an expanding intracranial lesion, such as rapidly diminishing visual acuity, marked reduction in visual fields, progressive extrinsic ocular defects, increasingly intense headaches, vomiting and convulsive episodes. The presence of endocrine abnormalities is by itself no indication for attempted removal of the tumor, both because the operative procedure is hazardous and because the likeli-

suprasellar calcification on x-ray examination of the skull and that the operation revealed a relatively solid craniopharyngioma with no calcific areas in the tumor tissue Because of the absence of both suprasellar calcification and enlargement of the sella turcica as well as the paucity of endocrine symptoms the correct histologic diagnosis was not suspected preoperatively However the existence of an intracranial tumor involving the hypophysis was postulated in view of the bitemporal constriction of the visual fields and the marked reduction in the basal metabolic rate

CASE 3 —The patient was a three and one-half year old boy who began to develop headaches three months prior to admission to the hospital These headaches were unusual in that they would begin at a specific time each morning and last for approximately the same length of time—four hours each day In this respect the headaches simulated those usually seen in sinusitis With the onset of the cephalgia it was noted that the patient developed a left external strabismus Two months after the onset of the headaches the patient began to complain of increasing thirst and frequency of urination and epigastric pain The latter symptom was always associated with the headache and vomiting and was followed by somnolence which lasted for an hour or so and resulted in relief of both the epigastric pain and the headache The child frequently experienced curious spells which no one else could detect

On physical examination the child appeared obese with rather slender extremities unusually small genitalia and was described by the intern staff as appearing hypopituitary in type There was moderate pallor of the optic discs a slight left central facial weakness and paresis of the upper and lower left extremities Visual field examinations revealed a reduction in visual acuity with a left temporal field defect

X-ray examination of the skull showed an enlarged sella turcica with marked erosion of the posterior clinoid processes There were several small calcific concretions both within and above the sella turcica

In view of the rather characteristic clinical and roentgenologic findings the patient was operated upon and the entire suprasellar portion of the craniopharyngioma was removed Within the course of the next few weeks the patient improved considerably and he was discharged from the hospital six weeks after the operation

During the next two years the patient remained relatively well He was free from headaches and epigastric pain although there occurred no improvement in vision and the Frohlich habitus became somewhat more pronounced Slightly more than two years after discharge from the hospital he was readmitted because of an acute right otitis media following measles The child's temperature was elevated to 106 F and pursued a septic course There was slight right mastoid tenderness Neurologic examination revealed the presence of bilateral optic atrophy and positive bilateral Oppenheim and Babinski signs

Following a jugular vein ligation with packing of the right transverse sinus the child developed several convulsive episodes and died seventeen hours after the operation

On autopsy a large cystic tumor measuring 2.5 cm in diameter was found occupying the interpeduncular space The cyst was thin walled and divided into pockets filled with a gelatinous material The microscopic study of sections of the cyst with hematoxylin and eosin stains showed a band of connective tissue lined with a thin layer of closely packed stratified squamous epithelial cells There were also collections of calcified lamellated bodies and hornified epithelial cells The adjacent fibrous tissue contained many round cells multinucleated giant cells and calcified blood vessel

Comment —This case represents a rather classical instance of a craniopharyngioma complete with endocrine and mechanical signs of an expanding intracranial mass enlargement and erosion of the sella turcica and

approximately seven years and the presence of both mechanical and endocrine symptoms are similar to the clinical picture observed in chromophobe tumors. The *presence of suprasellar calcifications on x ray examination* of the skull served to identify this case as an instance of craniopharyngioma rather than that of a chromophobe adenoma. The preoperative differentiation between the two groups of cases is dependent essentially on the roentgenologic presence or absence of suprasellar calcification. In addition peripheral neurologic abnormalities such as facial paresis or paralysis, the presence of a positive Babinski sign, *etc* occur much more commonly in craniopharyngiomas than they do in chromophobe adenomas.

The endocrine symptoms produced by the craniopharyngiomas are due essentially to pressure on the adjacent hypothalamus and hypophyseal tissue. The tumor tissue itself lacks any endocrine function. The polydipsia and polyuria that this patient manifested were in all probability due to hypothalamic involvement, while the cachexia, loss of pubic and axillary hair and amenorrhea were possibly the result of pressure destruction of the anterior hypophysis.

The endocrine symptoms were much less prominent than the mechanical symptoms which resulted from the expanding intracranial mass, and it is the severity and progression of the latter symptoms which determine whether such a patient should or should not be operated upon. The improvement which followed *x* ray therapy in this instance was unusual although short lived. In general the craniopharyngiomas, in contrast to the *chromophobe adenomas, fail to respond to such therapy.*

Case 2.—The patient was a fifty four year old man who was apparently well until six months before admission to the hospital, when he began to experience increasing fatigue, drowsiness, severe frontal headaches, blurring of vision and diplopia. On examination there was impairment of vision in both eyes and bilateral constriction of the temporal visual fields. The remainder of the physical examination was essentially negative. The basal metabolic rate was -33 per cent, while a complete peripheral blood cell count and differential study was quite normal. A spinal fluid examination revealed no abnormalities. X ray examination of the skull showed no enlargement of the sella turcica and no suprasellar calcifications. On operation a large firm tumor was found on the floor of the right lateral ventricle. Following the removal of the tumor *the patient developed a left hemiparesis. The temperature rose to 103° F*, the patient lapsed into coma and died on the second postoperative day.

The specimen removed at operation appeared solid and lobulated, although there were some small cystic areas *surrounded by a thin membrane. Histo*logical examination of the tissue with hematoxylin and eosin revealed densely cellular tumor tissue consisting of irregular collections of stratified squamous epithelium with a well defined basal layer surrounding large cores of loose connective tissue containing a moderate number of thin walled blood vessels. The connective tissue was made up essentially of loosely arranged fusiform cells, among which were infiltrating small round cells, polymorphonuclear leucocytes, phagocytic cells and round empty spaces having the appearance of vacuoles. On autopsy the hypophysis appeared grossly to be normal, but on microscopic study there were large necrotic areas in the adenohypophysis *with infiltration* with polymorphonuclear leucocytes.

Comment.—The noteworthy features of this case are the comparatively late age of onset of the disease and the relatively short duration of the symptoms. It is important to note too that there were no evidences of

thyroid gonads and adrenal cortices This is explained by the fact that the eosinophilic tumor may act as an irritative stimulus to the surrounding adenohypophyseal cells resulting in increased elaboration of thyrotropic gonadotropic and adrenocorticotropic factors Eventually however exhaustion of the pituitary cells may occur and varying degrees of hypopituitarism ensue This is particularly true when hemorrhage into or cystic degeneration of the eosinophilic tumor occurs with a comparatively sudden expansion in the size of the tumor and compression and atrophy of adjacent hypophyseal cells Similarly an adequate increase in the size of the tumor may result in encroachment on the hypothalamus with the appearance of obesity polydypsia and polyuria

Signs and Symptoms of Acromegaly — Acromegaly is a relatively uncommon disease occurring once in every 15 000 hospital admissions according to Putnam and Davidoff [34] In our own series at the Mount Sinai Hospital the incidence of the disease was 1 in every 6 200 hospital admissions Actually the incidence is probably considerably greater It must be remembered that the patients who seek admission to the hospital generally manifest the full blown picture frequently with evidence of an expanding intracranial mass The less complete cases frequently never gain admission to the hospital for study From the histological point of view eosinophilic adenomas constitute 20 per cent of the pituitary adenomas [7]

This is a disease essentially of adult life although some instances of the disease have been reported in adolescence and one case in a child of 8 [35] In one half the instances the early manifestations of the illness were noted during the third decade [34] The disease occurs with approximately equal frequency in males and females

Acromegaly is characterized essentially by an overgrowth of the terminal portions of the skeleton and of the soft parts and viscera as well as protean endocrine and psychic changes In addition the mechanical signs of an expanding intracranial mass are frequently present The initial symptoms are variable The earliest complaints may be easy fatigability asthenia vague nervous symptoms diffuse aches and pains and severe sweating These symptoms may precede the more characteristic manifestations by a considerable period of time Generally the first manifestations are an increase in the size of the head or hands and feet The patient notices that he requires a progressively larger hat or larger sized gloves and shoes Less commonly the earliest signs are amenorrhea or less pronounced disturbances in the menstrual cycle in the female and impotentia and loss of libido in the male The disease progresses slowly and insidiously and many years may elapse before the complete and characteristic clinical picture is present

The patient with the fully developed disease presents a striking appearance which when once seen is never forgotten The hands become large due to a broadening and thickening of the fingers and palms so that they assume a spade like appearance They feel stiff and clench with some difficulty The facial features coarsen the lips thicken while the nose becomes large and bulbous The head increases in size and the supraorbital ridges become prominent and overhanging There occurs a protrusion of the lower jaw the so-called prognathism due essentially to thickening and

suprasellar calcifications Of unusual interest is the early age of onset in contrast to the case previously cited

EOSINOPHILIC (ACIDOPHILIC) TUMORS OF THE ADENOHYPOPHYSIS—ACROMEGALY GIGANTISM

Active clinical interest in the disease acromegaly dates back to the classical description of Marie in 1886 [8] This author observed 2 cases characterized by *an increase in the size of the hands feet, and head a coarsening of the features of the face with prognathism broadening of the nose and thickening of the lips* In addition in this early report he included 5 cases which he collected from the literature and which had appeared under a variety of names He named the disease acromegaly The following year Minkowski [9] reported a case of acromegaly with a pituitary tumor to which the disease was ascribed Some years later Benda [3, 4] reported 3 cases of pituitary tumor with acromegaly and pointed out the predominance of the acidophilic cells in these adenomata This finding was subsequently confirmed by Fischer [5] The significance of the relationship of the eosinophils to the disease however was not fully accepted until comparatively recently [6]

Precisely when the relationship between gigantism and acromegaly was recognized is not entirely clear In 1895 Brissaud and Meige [7] suggested *that acromegaly and gigantism were due to the same pathological process* Several years later Hutchinson [8, 9] reported 3 cases of gigantism with necropsy studies in all of which a neoplasm of the adenohypophysis was found Subsequently Launois and Roy [10] collected a larger series of cases in which they demonstrated that pituitary tumors were present in all true cases of gigantism

It is now recognized and accepted that acromegaly and gigantism are due to increased secretory activity of the eosinophilic cells of the adenohypophysis Most commonly such increased secretion is due to eosinophilic tumors Much less frequently the disease is associated with hyperplasia of these cells or an increase in their number without actual tumor formation [23] The eosinophilic cells are actively secretory cells and in the light of the clinical abnormalities which result from their overactivity it is assumed that they are concerned with the elaboration of a growth or somatotropic factor There is some laboratory evidence available which confirms this clinical impression Thus the adenohypophysis of hereditarily dwarfed mice contains no eosinophilic cells [31, 32]

As to whether a patient with an eosinophilic tumor will develop acromegaly or gigantism is dependent essentially on the age of onset of the pathologic process *If the tumor develops in young people before epiphyseal union occurs gigantism results* A similar pathologic process in adults after the epiphyses have united will cause acromegaly Not infrequently the disease may begin during adolescence and continue actively into adult life In such instances the resultant clinical picture represents a combination of both states so-called *acromegalic gigantism*

The clinical picture of gigantism and acromegaly is not infrequently associated with increased activity of other endocrine glands notably the

disease the libido is increased but as the illness progresses libido and potentia become progressively less and frequently disappear entirely But occasionally throughout the course of the disease there may be a strikingly abundant spermatogenesis[37] Putnam and Davidoff[34] have described persistent lactation not related to an antecedent pregnancy This phenomenon occurred in approximately 5 per cent of their female patients

Generally speaking the ovaries and testes become atrophic during the course of the disease but this is by no means universally true Hypergenitalism not infrequently occurs in the male acromegalic and hypertrophy of the female genital tract has been described[38] Atrophy of the gonads is however, more common The ovaries become sclerotic and show cystic changes[38] Some investigators have described total regression of the primordial follicles and cessation of formation of the Graafian follicles[39] In the testes these same authors have observed degeneration of both the interstitial cells and the epithelium of the seminal vesicles In a little over one third of 118 women with acromegaly, atrophy of the uterus and adnexa was noted by another observer[40]

The Thyroid —Enlargement of the thyroid gland is frequently observed A review of the literature reveals that such enlargement occurs in one-fourth to one-half of the patients[41-4] As a rule, the goiter is diffuse and nodular On examination after operative removal the gland shows the presence of extensive cystic changes in a colloid gland with accumulation of large amounts of colloid in the cysts In addition there may be present localized nodules of variable size made up of hypertrophied thyroid tissue According to Atkinson[25] of 141 cases of acromegaly, the thyroid was hypertrophied in 57 per cent cystic in 19 per cent normal in 16 per cent and atrophied in 7 per cent

The reported incidence of actual hyperthyroidism in acromegaly is variable Davidoff[41] reports that in 100 patients with acromegaly 70 per cent showed an increase in the basal metabolic rate while only 50 per cent showed an enlargement of the thyroid Boothby and Sandiford[42] found an increase in the oxygen consumption in 15 of 30 cases with acromegaly In contrast to these observations Davis[4-] noted hyperthyroidism in only 3 of 166 instances of acromegaly while enlargement of the thyroid was seen in 52 per cent of the total In our own group at the Mount Sinai Hospital of 28 patients with well-defined acromegaly an elevated basal metabolic rate was observed in only 4 instances of which 1 had the definite clinical picture of hyperthyroidism In 7 patients with acromegaly with increaesed basal metabolic rates the thyroidal uptake of I_{131} was found to be low or normal[118]

It becomes obvious on a review of the literature that there is a good deal of confusion in terms of identifying clinical hyperthyroidism with an increase in the basal metabolic rate The latter apparently occurs with a greater degree of frequency than the former Slight increases in oxygen consumption occur with a considerable degree of frequency in acromegaly but the definite clinical manifestations of an overactive thyroid are uncommon It must be remembered that these patients have many nervous symptoms which may loosely be interpreted as hyperthyroid in character Exopthalmos is uncommon but here too the overhanging brows often

overgrowth of the mandible As a result, the teeth become widely spaced and override the upper dentition The tongue becomes large and coarse and thick The patients frequently develop a stoop due to kyphosis associated with enlargement and thickening of the vertebræ The skin generally hypertrophies and thickens loses its elasticity, and appears wrinkled and ridged Hypertrichosis is not uncommonly seen particularly in the female The visceral organs frequently although not always participate in the enlarging process The splanchnomegaly particularly involves the heart liver kidneys and spleen The intestines may become larger and longer and indeed a doubling of the intestinal length has been described [33]



Fig 4—Male acromegalic aged 30 years

Marked psychic changes often occur [35] The patients are emotionally unstable They tend to cry readily become unduly irritable and occasionally even maniacal They are sullen and vacillating although mentally quite alert and normally endowed It is of course difficult to know whether the psychic changes are a primary manifestation of the disease or whether they occur secondary to the marked cosmetic changes and the general feeling of ill being from which these unfortunate patients suffer

The Endocrine Manifestations of Acromegaly—*The Gonads*—Menstrual irregularities are exceedingly common According to Davidoff[8] irregularities of uterine bleeding occurred in 87 per cent of the female patients with acromegaly, while amenorrhea occurred in almost three fourths of them Atkinson[35] has pointed out however that pregnancy occurring during the course of the disease is not uncommon Slightly more than a third of the women have a diminished libido [36] The situation in this respect in the male patients is somewhat different Early in the course of the

clear-cut evidence of hyperthyroidism, acromegalic symptoms had been present for from seven to twenty-nine years.

A low basal metabolic rate occurs with a lesser degree of frequency in acromegaly than does an increase in oxygen consumption. In general, the symptoms of hypothyroidism are comparatively mild and contribute relatively little to the patient's discomfort.

The presence of hyperthyroidism or hypothyroidism in acromegaly is not particularly astonishing. The adenohypophysis elaborates a thyrotropic principle which acts on the thyroid gland. The presence of an eosinophilic tumor may act, on the one hand, as an irritative stimulus to those cells concerned with the secretion of thyrotropic hormone, or, on the other hand, may eventually produce pressure atrophy of the cells. In the first instance the signs and symptoms of hyperthyroidism will result, whereas in the second instance hypothyroidism will ensue. Actually, this is somewhat an oversimplification of the problem, since the microscopic picture of the thyroid frequently shows the simultaneous presence of hypertrophic nodular areas in an otherwise degenerated colloid gland.

The Adrenals.—The adrenals are usually enlarged in acromegaly. Actually, most of the enlargement is due to hypertrophy of the adrenal cortex. The medulla is only occasionally hyperplastic, but just as often this part of the gland may be perfectly normal or even show degenerative changes.[41] In addition, the gland often shows the presence of cortical adenomas. These tumors, which vary considerably in size, may be solitary but are frequently multiple and are scattered throughout the substances of the cortex. These hypertrophic changes in the adrenals are not particularly astonishing in the light of our present knowledge of adenohypophyseal function. Over two decades ago Putnam and his coworkers[46] noted the presence of adrenal cortical adenomas in dogs whom they attempted to make acromegalic by the prolonged daily injection of a rather crude alkaline extract of the adenohypophysis. During the next number of years this observation was repeatedly confirmed by various investigators employing partially purified anterior pituitary extracts.[47,48,49] All had noted adrenal cortical hypertrophy and often adrenal cortical adenomas following the use of their extracts over a long period of time. As discussed in the previous chapter, we now know that this effect on the adrenal cortex is due to the increased secretion of the adrenocorticotropic hormone by the adenohypophysis.

It is interesting to note that the adrenal cortical hypertrophy so commonly seen in acromegaly is accompanied by a paucity of those clinical findings ordinarily associated with increased adrenal cortical function. These patients rarely show any disturbances in electrolyte metabolism. The urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated steroids is generally normal, occasionally slightly decreased, and sometimes slightly elevated, while hypertension is an uncommon finding. In our group of 28 patients the blood pressure was definitely elevated in only 1 instance and questionably so in another. On the other hand, the increase in hirsutism and the disturbance in carbohydrate metabolism, both of which occur rather commonly in acromegaly, may perhaps be interpreted as evidence of adrenal cortical hyperfunction. The hirsutism in female acromegalics is, of course,

convey an impression of ocular prominence which actually is not present. With the development of better techniques *for blood iodine determinations* and with the use of urinary excretory studies of radioactive iodine administered in tracer doses the presence or absence of hyperthyroidism will be determined with a greater degree of accuracy.

The results of the treatment of the hyperthyroidism are interesting. The patient in our group responded in an orthodox manner to the administration of iodine and subsequent subtotal thyroidectomy. Prior to treatment this patient had episodes of paroxysmal auricular fibrillation, a persistent tachycardia, weight loss, *profuse sweating*, and a basal metabolic rate of plus 28 per cent. Following three weeks *of therapy with Lugol's* solution in a dosage of 10 drops 3 times a day there occurred a marked improvement. The basal metabolic rate was reduced to plus 10 per cent, while the pulse rate fell considerably. There was an adequate gain in weight and a marked improvement in the nervous symptoms. Within four weeks after subtotal thyroidectomy, the basal metabolic rate had fallen to plus 1 per cent, while the episodes of auricular fibrillation had entirely disappeared. On the other hand, of the 3 cases reported by Davis[4] treated with iodine, only 1 showed a moderate decrease in the oxygen consumption, while the response to subtotal thyroidectomy was less constant and less in degree than in non-acromegalic patients with hyperthyroidism. Cushing and Davidoff[44] found that iodine induces a remission in hyperthyroidism associated with acromegaly similar to that obtained in ordinary exopthalmic goiter. However, the results of subtotal thyroidectomy in the acromegalics were not entirely satisfactory, while the removal of the hypophyseal adenoma was followed by a decrease in the basal metabolic rate almost as satisfactory as that obtained after subtotal thyroidectomy in patients with exopthalmic goiter. In general, thyroidectomy is not an innocuous procedure in acromegaly. Of 27 instances in which subtotal thyroidectomy was performed there were 5 fatalities.[4] Friedgood[45] reported 2 instances of hyperthyroidism in acromegaly which responded in a satisfactory orthodox fashion to iodine therapy.

In summary, then, patients with acromegaly frequently show enlargement of the thyroid and often present an increase in the basal metabolic rate. Generally speaking, the increased oxygen consumption is relatively moderate. Only infrequently is there definite clinical evidence of hyperthyroidism, *while exopthalmos is quite uncommon. The response to iodine* therapy and subtotal thyroidectomy is variable. Most of these patients respond fairly well to Lugol's solution, but some react inadequately. Subtotal thyroidectomy always produces some improvement in the hyperthyroid state. In some instances the remission is complete, while in others the response is not as good as that obtained in exopthalmic goiter. Following the satisfactory removal of the hypophyseal tumor there apparently occurs a disappearance of the hyperthyroidism.

The development of hyperthyroidism may occur at any stage of the disease. In 1 patient the symptoms of hyperthyroidism appeared twenty years after the onset of the acromegaly. In the remaining 5 patients in whom there occurred an increase in the basal metabolic rate without any other

The Thymus.—Atkinson[34] described a persistent thymus in 54.6 per cent of 98 cases of acromegaly. The enlargement of the thymus sometimes plays an important role in the outcome when the acromegalic is subjected to a surgical procedure. Goldberg and Lesser[6] describe a patient with acromegaly who died during anesthesia prior to operation for a pilonidal cyst. On postmortem examination the thymus was found to be markedly enlarged.

Skeletal Changes.—The skull and the extremities are most commonly involved in acromegaly. Somewhat less frequently the vertebral column participates in the pathologic process. The essential characteristic of the bony changes consists of an overgrowth of the bones, mostly in their transverse diameter. The bones become thickened and broad and sclerotic and the trabecular structure prominent. The increase in the size of the head is due to an increased thickness of the flat bones of the skull, an enlargement of the external occipital protuberance, marked enlargement of the frontal and nasal sinuses as well as the mastoid cells. The supraorbital ridges become prominent, while the enlargement of the mandible results from the overexpansion of this cancellous bone. In the extremities there occurs an increase in periosteal bone growth, as well as expansion of the cancellous bone. Often the cartilagenous tissue becomes ossified.[37] The terminal phalanges particularly tend to become thickened with the formation of irregular exostosis producing the fairly characteristic "tufting" so commonly seen in acromegaly. The dorsal vertebrae become irregularly enlarged, especially in their transverse diameter. There is an increase in the antero-posterior diameter of the chest, a dorsal kyphosis, and sometimes a compensatory lumbar lordosis.

The bones which are involved in the process are hard, thick, and irregular, with numerous exostoses. The blood channels are markedly dilated.[58]

The roentgenologic study of the skeleton reveals the characteristic thickening of the bones. Of prime importance is the demonstration of enlargement of the sella turcica. This occurred in all but one of our cases and in 87 per cent of the patients described by Davidoff.[41] The posterior clinoid processes are often involved, and when the tumor expands upward they become eroded and sometimes completely destroyed. The x-ray presence of "tufting" of the terminal phalanges, although not entirely pathognomonic of the disease, is strongly suggestive of it. The diagnosis of an eosinophilic tumor is established beyond doubt when x-ray studies reveal enlargement of the sella turcica, increase in width and hardness of the bones and "tufting" of the terminal phalanges of the fingers or toes.

Arthritis sometimes occurs in acromegaly. The joint changes are indistinguishable from those observed in hypertrophic arthritis and are characterized by the appearance of many osteophytes. In addition, Erdheim[59] described joint changes associated with periosteal ossification and irregular proliferation of the joint cartilage.

The skin, muscles, connective tissue, and mucous membranes also participate in the disease process. The skin becomes coarse, thickened, and inelastic, and is readily separated from the underlying tissue. The sebaceous glands are enlarged, the hair follicles increase in size, and the papillae become hypertrophied. The skin, especially of the exposed parts, often

in evidence of virilism and in several instances enlargement of the clitoris has been noted[51] The classical adrenogenital syndrome and the Cushing syndrome however so frequently observed in adrenal cortical tumor, or adrenal cortical *hyperfunction associated with a pituitary basophilic tumor* is not seen in acromegaly except as a most unusual rarity Later in the course of the disease, asthenia and marked muscular weakness are frequently seen Although these symptoms are not associated with any reduction *in the serum sodium or an increase in the urinary excretion of this* electrolyte the response to the parenteral administration of whole adrenal cortical extract is often gratifying This would suggest that some degree of adrenal cortical exhaustion probably does take place

Carbohydrate Metabolism — The disturbance in carbohydrate metabolism is probably related to the disturbance in adrenal cortical function as well as to the diabetogenic effect of growth hormone The existence of such a relationship is essentially speculative at the present time It is suggested however by the fact that the regulation of the diabetes of the acromegalic is difficult The diabetes of these patients is notoriously resistant to even rigid dietary control and their response to insulin is by no means entirely satisfactory The diabetes will occasionally disappear spontaneously generally during the later course of the disease when evidence of adenohypophyseal hypofunction is evident

True diabetes occurs in perhaps 10 per cent of the patients, while glycosuria occurs in approximately half[5] In our series hyperglycemia occurred in approximately 20 per cent of the patients, while a decrease in glucose tolerance as demonstrated by glucose tolerance curves occurred in almost a third

The Parathyroids —An elevation of the serum inorganic phosphorus is not infrequently observed[22] This is however only rarely associated with a decrease in serum calcium These findings are rather surprising in view of the pathologic changes which are sometimes observed in the parathyroids in this disease Erdheim[53] originally described enlargement of the parathyroids in acromegaly and even parathyroid adenomas have been noted[54, 55]

Crude adenohypophyseal extracts have produced both hyperplasia and adenomas of the parathyroids in experimental animals[34, 56, 57] In the light of these experimental and histological studies we might expect that patients with acromegaly would show some evidence of increased parathyroid function Clinically this is apparently not so while serum calcium and phosphorus studies reveal rather the antithesis Tornblom[119] has suggested that the elevated serum inorganic phosphorus may be responsible for the parathyroid hyperplasia

Hypothalamic Symptoms —Polyuria and polydipsia occur in approximately 25 per cent of the cases[41] independent of the presence of hyperglycemia or glycosuria Approximately a third of the patients show a considerable weight gain while a somewhat smaller number have voracious appetites[41] Somnolence not infrequently occurs particularly early in the disease These symptoms which are perhaps hypothalamic in origin are probably due to pressure on this area by the expanding pituitary tumor and in this sense are not specific since they may be elicited by any type of pituitary mass encroaching on the hypothalamus

becomes pigmented due to increased deposition of melanin. The underlying connective tissue increases in amount and at least early in the course of the illness the muscles are hypertrophied. Later the muscles degenerate, become atrophic and are infiltrated with connective tissue and fat.[80] The mucous membrane of the mouth is thickened while the tongue is increased in size because of the hypertrophy of its muscle and papillae. The larynx is enlarged and the vocal cords thickened and elongated.

Laboratory Data in Acromegaly.—The peripheral blood count and differential studies fail to demonstrate any characteristic findings in acromegaly. The hemoglobin and red blood cell count are generally quite well within the normal range and only infrequently is a normocytic anemia observed, rarely of any severe degree. The total white blood cell count is usually normal but sometimes slightly reduced, while the differential study tends to show a moderate lymphocytosis. Acromegaly is not characteristically associated with any evidence of impaired renal function. The urea nitrogen levels are not elevated, the total proteins and albumin-globulin ratios are within the normal range and the various tests of renal function show no abnormalities. As mentioned elsewhere in this chapter the serum inorganic phosphorus is sometimes elevated but no abnormalities are usually observed either in the calcium levels or the serum alkaline phosphatase values.

The changes in the spinal fluid in acromegaly are dependent on the size of the pituitary tumor and the presence of increased intracranial pressure. In most instances the spinal fluid dynamics, chemistry and counts are perfectly normal. Where the tumor is large enough to produce a considerable increase in intracranial pressure there may be some elevation in spinal fluid pressure with a slight increase in spinal fluid proteins and some pleocytosis.

The daily urinary excretion of the neutral 17 ketosteroids and the 11 oxygenated steroids is variable in acromegaly. These may be normal, slightly decreased or slightly elevated. In general a slight increase in the 17 ketosteroids is more frequently observed to occur in the male than in the female acromegalics. In 40 collected cases of acromegaly in which the daily urinary excretion of the neutral 17 ketosteroids was determined the results were normal in 18, slightly elevated in 11 and slightly decreased in 11. Rarely did the daily urinary excretion exceed 26 mgm. or fall below 4.0 mgm. The 40 cases consisted of 17 male patients and 23 females. Of the former group in 8 the daily urinary excretion of the 17 ketosteroids was slightly elevated, 4 were within the normal range and in 5 the values were slightly reduced. In the group of female patients 3 were slightly elevated, 14 normal and 6 yielded results slightly below normal.[50, 90, 97, 98, 99]

The urinary excretion of the pituitary gonadotropins (follicle stimulating hormone) is generally normal. A slightly reduced value is however not infrequently obtained but only rarely are the values elevated. Thus of 18 acromegalics in whom the daily urinary excretion of pituitary gonadotropins was measured, 9 yielded perfectly normal values, in 7 the values were somewhat low and only in 2 definitely elevated.[97, 98]

Non Endocrine Symptoms in Acromegaly.—In addition to the signs and symptoms which are related to increased or decreased secretory activity

Fig. 5.—Acromegaly. Note the elongation of the mandible, large sinuses and enlargement of the sella

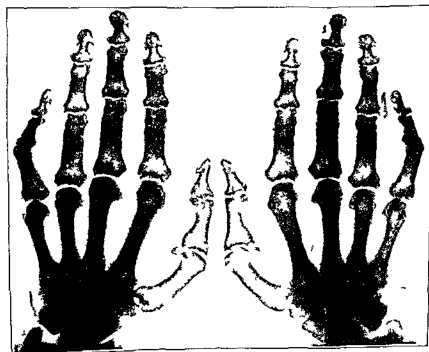


Fig. 6.—Acromegaly. Note the enlargement of the terminal phalanges

(2) the symptoms due to the mechanical effects of an intracranial mass. The endocrine symptoms are due to increased secretion of the eosinophilic cells of the adenohypophysis and the pressure effects of the tumor on the surrounding anterior pituitary cells and hypothalamus. Thus the patients will often present, in addition to the evidences of hyperpituitarism, hypothalamic and hypopituitary manifestations. The most common characteristic of the disease is the enlargement of the acral parts of the skeleton. The bones of the skull and extremities become thickened and enlarged; there is an overgrowth of the supraorbital ridges and lower jaw. The vertebra are widened, the chest barrel shaped, and a dorsal kyphosis is often present. The skin and soft parts participate in the hypertrophic process. The tongue is large and the visceral organs are often increased in size. The basal metabolic rate is frequently increased, the thyroid palpable, and definite clinical evidences of hyperthyroidism sometimes present. Occasionally symptoms of hypothyroidism are evident. Disturbance in carbohydrate metabolism as evidenced by glycosuria, hyperglycemia and a diabetic glucose tolerance curve is often encountered. Actual diabetes mellitus occurs in about 10 per cent of the cases. Polyuria, polydypsia and polyphagia can occur independently of the disturbances in carbohydrate metabolism and are probably hypothalamic in origin. Profuse perspiration is common. In males, macrogenitalism is often observed early in the disease, but later the testes may show considerable atrophy, and loss of libido and impotentia are common. Disturbances in menses and amenorrhea are frequently seen in females. Hypertrichosis occurs in both males and females.

TABLE 5.—ENDOCRINE EFFECTS OF ACIDOPHILIC ADENOMAS BASED UPON AN ANALYSIS OF THE RECORDS OF 100 CASES FROM CUSHING'S SERIES AND TABULATED BY DAVIDOFF[41]

	Per cent
Enlargement of acral parts (gigantism 14 cases)	100
Disturbance of menstrual cycle	87
Amenorrhea	73
Increased BMR	70
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Gain in weight	39
Diminished libido	38
Asthenia	33
Low blood pressure (less than 120 systolic)	30
Polyphagia	28
Fibromata mollusca of skin	27
Polydypsia	25
Enlarged thyroid	25
Glycosuria (diabetes mellitus 12 cases)	25
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4

The non-endocrine signs and symptoms are related to the mechanical presence of an intracranial mass and include headache, disturbances in vision, vomiting and in general evidence of increased intracranial pressure

of the adenohypophyseal cells patients with acromegaly frequently manifest the evidences of an expanding intracranial neoplasm These symptoms are by far and large no different from those produced by any pituitary neoplasm endocrine or otherwise and are related to the mechanical effects of the tumor Headache occurs quite frequently and according to Putnam and Davidoff,[34] is present in 90 per cent of the patients In our experience this symptom has occurred less frequently but is present in approximately 50 per cent of the cases The headaches are generally bitemporal or frontal, and may vary considerably in severity They may appear early in the course of the disease and not change in character or intensity for many years On the other hand the intensity of the headaches may progress very rapidly, be continuously present and force surgical intervention The mechanism of the headaches is not always entirely clear in acromegaly In general we must distinguish two groups In one the cephalgia is due to an expanding pituitary mass which increases the intrasellar tension and produces bulging of the diaphragma sella In this group of patients operation will induce prompt and satisfactory relief, similar to that obtained following operation for a chromophobe adenoma Occasionally these headaches will subside spontaneously as the tumor ruptures through the diaphragma sella thus automatically relieving the pressure within the sella But in another group of patients severe headache may be present with a perfectly normal sella with no evidence of involvement of the chiasm and no signs of bulging dura In such patients operation may not afford immediate relief In this group, as Henderson points out [14] the headache is generalized all over the head and is probably due to the participation of the bones of the skull, sella and meninges in the general acromegalic proliferative process This type of headache is, therefore endocrine rather than mechanical in origin

Some visual defects occur in approximately two-thirds of the patients These defects may consist of loss of acuity of vision, blurring diplopia restriction of visual fields both for color and form bitemporal and homonymous hemianopsia There may be unilateral or bilateral optic atrophy with or without papilledema The visual defects produced by an adenohypophyseal tumor are due to pressure of the mass on the overlying optic chiasm This pressure is first exerted on the posterior portion of the chiasm producing a defect in the superior temporal quadrants of the visual fields Later as the tumor increases in size complete bitemporal hemianopsia results Finally with further growth of the tumor the nasal portions of the visual fields may become impaired [66]

In general the mechanical symptoms of an intracranial mass with increased intracranial pressure are as frequent as those observed in chromophobe adenomas and in craniopharyngiomas but tend to be less severe and to progress less rapidly Most acromegalics may continue with relatively minor manifestations throughout the course of the illness But as with the other two diseases, a rapid uncontrollable intensification of the symptoms of increased intracranial pressure may occur and call for prompt surgical intervention

Summary of the Clinical Picture of Acromegaly — The clinical symptoms of acromegaly fall into two categories (1) the endocrine symptoms and

failure 3 from cerebral accidents and in 5 the exact cause of death was unknown

A summary of the general causes of death in acromegaly would include the following

1 Intracranial extension hemorrhage and degeneration of the tumor
2 Diabetes mellitus and its associated hazards
3 Cardiac failure
4 Intercurrent infections
5 Attempted surgical removal of the tumor
6 Cachexia

It is important to emphasize that at best the acromegalic is not a very good surgical risk and any reasonable major operative procedure should be decided upon with a good deal of caution

In our own group of patients there was a surprisingly high incidence of recurrent renal calculi and bleeding duodenal ulcer, 11 per cent of each This is considerably above the statistical expectancy

The Treatment of Acromegaly — There are two aspects of the treatment of acromegaly *i e* the treatment of the disease itself and the symptomatic handling of some of its manifestations such as hyperthyroidism diabetes mellitus and hypopituitarism

There are 3 therapeutic measures available for the treatment of acromegaly (1) X ray therapy to the hypophysis (2) surgical removal of the tumor and (3) the use of estrogens and perhaps androgens in an effort to inhibit adenohypophyseal activity

X ray Treatment —In 1909 Gramegna[67] reported the first case of a pituitary tumor treated by irradiation The patient was a forty five year old woman with marked acromegaly Gramegna employed only one portal through the mouth and gave the patient 2 treatments a week for four weeks Eight to 9 Benoist units were given at each treatment The therapy was followed by a rapid although transient objective and subjective improvement Seven months later the symptoms recurred and another series of treatments was given with less marked beneficial effect In 1922 Beclere[68] published a follow up report of a sixteen year old girl with gigantism due to pituitary tumor whom he had treated with irradiation thirteen years earlier She had had severe headaches marked impairment of vision and the sella turcica was considerably enlarged Following a single course of radiotherapy the headaches disappeared the vision improved and she continued perfectly well to the time of the report thirteen years later This was the first instance of an apparent cure by *x* ray therapy The author employed both temporal fields for portals Both Gramegna and Beclere used exceedingly small doses

Since those early days irradiation of the pituitary for acromegaly has advanced considerably and become a well-established procedure Apparatus and techniques have improved the dosage considerably increased and hazards to the patient reduced Dott and Bailey[1] reported on 162 hypophyseal adenomata of all types treated with surgery and *x* ray They felt that roentgen therapy had been of definite value and suggested its use unless there was imminent danger of loss of vision in which event surgery was to be preferred Where operative intervention was necessary

Course and Prognosis — The course of events in acromegaly is variable. It is determined essentially by the size of the tumor, its compressive effect on contiguous secretory cells and non-endocrine tissue, and the degree of secretory activity of the eosinophilic tumor cells. A large and growing tumor subjects the patient to all the hazards generally associated with an expanding intracranial neoplasm. In addition to the visual defects resulting from pressure of the mass on the optic chiasm, death due to the intracranial pressure effects of a large eosinophilic tumor have been described.[6]

The pressure atrophy of the surrounding secretory cells, as well as the exhaustion of the tumor cells themselves, will result in many manifestations of hypopituitarism. Rarely, the patients may develop extreme cachexia similar to that observed in Simmonds' disease, although this phenomenon is more likely to occur with other types of hypophyseal tumors.[63]

The duration and the severity of the disease will depend on the factors described above. In general, patients with eosinophilic hyperplasia rather *than tumor run a much more moderate course.* By far and large most patients with acromegaly pursue a prolonged course lasting from five to thirty and even to fifty years.[20] In our series of patients the illness has lasted from six to twenty-nine years. Although the disease is usually associated with progressive incapacitation, there are many patients who remain quite well both mentally and physically for many years and are not particularly handicapped except for their startling appearance. Occasionally spontaneous remissions will occur in which the headaches will disappear, weakness and fatigability subside, and adequate gonadal function will be resumed. There may even be a slight improvement, although no real regression, in the physical appearance. On the other hand, a rapid progression of the symptoms may follow hemorrhage into the tumor.

The acromegalic is subject to certain hazards, some of which are life threatening and which usually account for the fatalities in these patients. Death is commonly due to intracranial extension of the mass, hemorrhage and degeneration of the tumor with extension into the sphenoidal sinus,[65] diabetic coma, congestive heart failure, and to intercurrent infections, the latter particularly in the presence of hypopituitarism. Enlargement of the heart has frequently been observed in acromegaly, and its significance has been emphasized by Courville and Mason.[64] These authors reported evidence of congestive failure in 18 of 24 patients, 6 of whom died. The occurrence of irregularities of cardiac rhythm, especially auricular fibrillation, is not uncommon. Cushing and Davidoff[4] collected 44 autopsied cases from the literature and found that diabetic coma was the single most *important cause of death* and accounted for 11 fatalities. The next most common cause was cardiac failure with 7 deaths. In interpreting these results it must be remembered that the data reported by Cushing and Davidoff occurred during the early days of insulin therapy *and hence the* significance of diabetic coma is probably exaggerated. However, even today the diabetes mellitus occurring in the acromegalic is difficult to control adequately. In a more recent study Henderson[11] reported on 23 *acromegalic* fatalities and found that 7 patients died from intracranial extensions of the tumor, 6 from diabetes mellitus, 4 from acute myocardial

jury. A second course may be given in two months and repeated at five to seven month intervals if necessary. With this course of treatment Kaplan observed no permanent epilation and no evidence of damage to the brain or the normal pituitary.

Kerr and Cooper[66] employ five 6×8 cm portals about the head. Each of 2 portals is given 200 r daily using 200 kv. Thoraeus filtration 50 cm distance until each has received 1800 r or a total of 9000 r measured in air.

The acidophil tumors are generally more sensitive to radiotherapy than the chromophobe adenomas and perhaps less so than the basophilic tumors. In the radiosensitive tumors there is prompt symptomatic relief as evidenced by the cessation of headache, improvement of vision and widening of the visual fields. The headaches may begin to subside within a few hours after the initial treatment,[74] but more generally so after the first week. In some instances the response is delayed and improvement may not really be complete for a number of months.[76] In general, however, if improvement is not definite within six to eight weeks after conclusion of therapy it is unlikely that further relief will follow as a result of this first course of treatment. In addition to the cessation of the headaches and improvement in vision there is a diminution in the polydypsia and polyuria, a general sense of well being and an improvement in the mental outlook of the patient. There is no decrease in size of the sella or of any of the enlarged bones but there may be some diminution in the edema of the soft parts. The latter may result in some decrease in the coarseness of the features and a reduction in the hat size or glove and shoe size. The successful results of radiotherapy, however, are characterized much more by a relief of the mechanical symptoms resulting from an intracranial mass than by any change in the appearance of the patient.

Occasionally, with the beginning of treatment the headaches may become more pronounced, vomiting more frequent and visual disturbances more marked. This is evidence that the initial roentgen dose is too large and calls for a reduction with a subsequent gradual increase. Most radiotherapists feel that whether the patient improves or not after the first course of therapy a second similar course should be instituted within two or three months after conclusion of the first. The return of symptoms at any time calls for further irradiation.

The question has arisen as to whether radiotherapy renders possible subsequent surgical procedures more difficult. Henderson[11] has described an instance of extensive adhesions between the adenoma and the chiasm which prevented a satisfactory surgical removal of the tumor. These adhesions were attributed to intensive radiotherapy administered a considerable time prior to the operation. However, Grant,[1] who has had a large experience in surgery of pituitary tumors, has not encountered any great surgical difficulties as a result of preliminary radiotherapy. In any event it would appear that the surgical hazards resulting from prior radiotherapy are not so considerable as to preclude a trial course of irradiation where indicated.

The Surgical Treatment of Acromegaly.—The surgical removal of pituitary tumors dates back to Schloffer[65] in 1906 who attacked such a lesion through the endonasal or transphenoidal route. This technic was subse

they suggested that it be followed by x ray therapy in an attempt to retard further growth of remaining tumor tissue In addition to poorly classified pituitary tumors treated by irradiation there are 54 instances of classical acromegaly with enlarged sella treated with radiotherapy alone [69, 70, 71, 72, 73, 74] These represent cases reported by different investigators employing varying techniques and dosages and hence the conclusions are perhaps not too significant In any event approximately 54 per cent of this group responded very favorably to irradiation It is interesting to observe that a further analysis of these cases reveals that by far and large those patients that were treated with larger dosage of irradiation responded considerably better In 1 group of 26 patients reported by Vaughan [74] that were treated with a relatively small amount where the total irradiation dose was 2700 r only 2 yielded excellent results and in 8 others the results were good This represents a satisfactory result in a little over 38 per cent On the other hand both Kerr and Cooper[66] and Kaplan[75] reported much better results where the total irradiation dosage was 9000 r measured in air This represents a dosage of some 4500 r to the brain itself As a matter of fact both Towne[69] and Harris and Selinsky[7] feel that failure of an eosinophilic tumor to respond to an adequate amount of irradiation is evidence that such a tumor is probably cystic and therefore radioresistant

The argument advanced by Vaughan[74] against the use of the larger doses of irradiation is the fact that following even as small a dose as he employs the patients frequently develop post irradiation debility lethargy and increased susceptibility to infection These symptoms may last for a month or two after conclusion of radiotherapy The hazards of x ray treatment to the pituitary are real and must never be lost sight of Such dangers include principally brain edema acute hemorrhagic cyst formation and cataract formation These dangers as Sosman[76] points out are real although fortunately infrequent and to some extent can be minimized by suitable precautions and proper techniques The amount of x ray dosage generally capable of producing brain damage is considerably in excess of that usually employed in therapy Thus Sosman[75, 76] has emphasized that if more than 6000 r are given to the brain itself in any one series of consecutive treatments there is an approach to brain damage Brain damage results with over 6000 r while the use of 10 000 r to 12 000 r in the brain in one series may result fatally In children the safe limit is considerably lower, being 3000 to 4500 r in the brain in one course

The procedure which Kaplan[75] advocates is as follows The technic entails these factors—200 kv 20 ma 50 cm distance 0 5 mm copper and 1 0 mm aluminum filter portals 4 × 6 and 6 × 8 cm Treatment is delivered through 6 portals right and left frontal right and left temple bregma and vertex A daily roentgen dose consists of 150 r measured in air to each of 2 portals Treatments are given 5 or 6 times a week until a total dose of 1500 r is administered over each portal The average course of therapy entails a total dose of 9000 r measured in air and delivered to the scalp The average depth dose in the pituitary gland is approximately 50 per cent of the surface dose therefore within a period of about two months with such a course of radiation the pituitary should receive some 4500 r considerably less than the amount which would normally induce brain in

However it is important to emphasize that only rarely are the endocrine symptoms alone an adequate reason for subjecting the patient to the operation On the other hand the presence of progressive diminution of vision and severe intractable headaches which do not respond to radiotherapy call for surgical intervention Where the diminution in vision is acute and its progress rapid such patients should be promptly operated upon without subjecting them to a previous trial with x ray therapy

The improvement in the visual symptoms is generally more frequent and more marked than relief of the headache Of 12 patients with acromegaly operated upon by the Cushing group[14] in 4 normal vision was recovered in both eyes and in 7 others there was marked improvement Visual recovery may occur directly after operation but generally requires several weeks to reach a maximal peak Occasionally improvement may continue for a year or even two after operation[14] In addition to the improvement of the visual symptoms 10 of the 12 patients have enjoyed general good health up to the time of the publication of their report a period which varied from seven to twenty four years after the operation An occasional patient may require a secondary operation for recurrence of visual failure The recurrence of the symptoms is as a rule due to extension of the tumor generally into the temporal lobe

The results obtained by surgery for relief of the headaches are not nearly so satisfactory Where the headaches are associated with diminution of vision in the presence of a markedly enlarged sella the relief of the intrasellar pressure following removal of the tumor will result either in a disappearance of the headache or a marked improvement in this symptom However, where headache is present with normal vision and an only slightly enlarged sella surgical removal of the tumor will result in improvement of the headache much less frequently and less dramatically so Henderson[14] reports 13 such patients with acromegaly who were operated upon because of severe headache with normal vision and only slightly enlarged sellas The headache promptly disappeared after operation in only 2 cases In 6 patients the headache gradually decreased in severity during the course of the next several months while in the remaining 5 instances the headache remained completely unaffected Similarly the long term results were not as good as those observed in patients with impairment of vision who were operated upon Almost half of the patients died from the effects of the disease *within a comparatively short period of time after the operation*

The presence of headache alone never constitutes an urgent indication for surgery Consequently such patients should first be subjected to an adequate course of radiotherapy If there is no improvement in the headache following such therapy it is not likely that surgery will yield very much better results

The response of the cephalgia in acromegaly is quite different from that in chromophobe tumors In the latter the headache is always due to an increase in intrasellar pressure and surgical relief of such pressure generally results in a prompt and dramatic improvement This is often true in acromegaly too but just as often the headache in this condition is due not to an increase in intrasellar pressure but as part of the general disease process It is in this group that the results are not entirely satisfactory and are de

quently modified by a number of investigators including Cushing.[77] However, this extracranial approach has certain serious disadvantages which are evident particularly in attempts to remove chromophobe adenomas. For one thing, the exposure obtained with the transphenoidal approach is not entirely satisfactory, and the technical difficulties inherent in the procedure forced the development of an intracranial approach. In 1909 Krause[78] and in 1913 Frazier,[79] followed by Heuer in 1920[80] suggested an approach from above through the anterior cranial fossa. This transfrontal intracranial method with some minor modifications has become the accepted method for attacking most extrasellar or intrasellar tumors with the exception of the eosinophilic ones. The latter tumors are still best approached through the transphenoidal route. *The presence of enlarged* frontal air sinuses, so common in acromegaly, renders the transfrontal approach more hazardous in this disease.

Surgery of the pituitary tumor in acromegaly is in general more difficult than in the instance of other pituitary tumors. These surgical difficulties are due to two factors. In the first place, the frequency with which general diseases, such as diabetes, hyperthyroidism and cardiovascular disease, exist in acromegaly render any operative risk greater. And secondly, the nature of the bony changes in the skull in acromegaly increases the specific operative difficulties with its attendant greater risks. However, lest we get an exaggerated notion of the dangers of the removal of an eosinophilic tumor, the operative mortality rate reported by Henderson[14] on a group of 60 patients with eosinophilic tumors operated upon by Cushing and his group by the transphenoidal route was 6.6 per cent. This is in contrast to a mortality rate of 5.3 per cent on a group of patients with chromophobe adenomas operated upon by the same group through a transfrontal approach. The operative mortality on a much smaller group of patients with acromegaly operated upon through this route was considerably higher than through the transphenoidal operation.

In gauging the operative mortality risks of pituitary surgery, it must *be remembered that the data cited above represent the results obtained by* a highly skilled group. Certainly the risks vary from surgeon to surgeon, but in the good neurosurgical clinics in this country the operative mortality should not exceed 10 per cent.[1] With the improvements in neurosurgical technics which are constantly being developed, this figure is being approached in most clinics and lowered in many.

The complete surgical removal of a pituitary adenoma is usually impossible.[1] This is generally due to the fact that the vessels forming the circle of Willis surround the sella and are frequently adherent to the capsule of the tumor. Too radical an attempt at removal of the tumor may result in injury to and bleeding from these vessels.

The primary indications for the surgical removal of an eosinophilic adenoma are progressive loss of vision and severe headaches. Where surgery is successful these symptoms, or at least the visual disturbances, are dramatically relieved. As with x-ray therapy, the endocrine manifestations are only slightly improved, although further deteriorative changes resulting from continued hyperpituitarism may be halted. Both diabetes mellitus and hyperthyroidism, if present, may be cured by the removal of the tumor.

Hormonal Treatment of Acromegaly.—It has been known for a long time that gonadectomy is followed by hypertrophy of the adenohypophysis. Early in the 1930's Schrire and Zwarenstein, working with rabbits, reported that increased adenohypophyseal activity was associated with an increase in the urinary excretion of both creatine and creatinine and that reduction in such excretion followed injections of testicular and ovarian hormones. These investigators assumed, therefore, that the gonadal hormones inhibited the activity of the adenohypophysis. Some time later Schrire and Sharkey-Schafer observed that in 4 patients with acromegaly there occurred a similar increase in the urinary excretion of creatine and creatinine, although the daily excretion of these compounds fluctuated widely. Following the daily injection of 10 mgm. of estradiol benzoate for ten days into 2 female acromegalics and the daily injection of 100 mgm. of testosterone propionate for eight days into 2 male acromegalics, there occurred a prompt diminution in the urinary excretion of creatinine, although the creatinuria remained unaffected.

Kirklin and Wilder[55] treated 8 patients with acromegaly, 4 males and 4 females, with small doses of estrogenic hormone over a prolonged period of time and reported that "in every instance there was an appreciable clinical change—in some more than in others. Most noticeable was the relief of the headache when present, although improvement in the visual fields, reduction in the basal metabolic rate, and an increased sense of strength and well being were also observed. There occurred no change in the character of the bony structure, although, as with the other forms of therapy, the skin became softer and thinner and the soft parts shrank as the underlying edema subsided." These investigators employed Theelin and Amniotin in a dosage of 1000 to 2000 international units administered daily for approximately a month and then on alternate days thereafter for from three months to a year. Subsequently Marrian and Butler[56] showed that estrogens in small doses stimulated and in large doses inhibited pituitary activity. Frank[57] pointed out that this effect of the estrogens was particularly directed to the gonadotrophic activity of the adenohypophysis.

It seems well documented, therefore, that estrogens, at least, are capable of inhibiting adenohypophyseal activity to some degree. Nevertheless, subsequent clinical trials with this form of therapy in acromegaly were not nearly as encouraging as those obtained by Kirklin and Wilder and the results in general leave a good deal to be desired. In view of the relative innocuousness of the therapy, however, its trial where feasible is desirable. Hamblen[117] recommends the daily oral administration of 5 to 10 mgm. of diethyl stilbestrol given cyclically, that is, for twenty consecutive days of every month starting with the conclusion of the menses if they are present and stopping before the onset of the next bleeding episode.

The Treatment of the Secondary Manifestations of Acromegaly.—The major problems occurring in this group are the treatment of hyperthyroidism, diabetes mellitus, congestive heart failure, and the not infrequent evidences of hypopituitarism. A moderate elevation of the basal metabolic rate in the absence of other symptoms of thyrotoxicosis should not be accepted as evidence of hyperthyroidism. Where definite hyperthyroidism is present, however, the forms of therapy available are those which are

pendent on a recession of the hyperpituitarism incidental to the successful removal of the tumor In this group the improvement in the headache is slow and gradual and continues over a period of months

In summarizing the indications for surgical therapy and the results obtained these points should be emphasized

1 The major indications for surgical removal of the tumor are (a) *impending loss of vision, (b) severe intractable headache and (c) severe* and progressive acromegalic symptoms that do not respond to adequate radiotherapy

2 Visual recovery is consistently good and recurrences relatively infrequent Relief of headache is variable and is dependent on whether the symptom is due to increasing intrasellar pressure or is part of the general hyperpituitary process Where the sella is enlarged and visual disturbances are present relief of the headache will probably be prompt and satisfactory directly after the operation Where there are no visual disturbances and the sella is not particularly enlarged relief of the headache may be slow and gradual

3 The successful removal of an eosinophilic tumor will halt the hypersecretory process and induce some recession in the acromegalic manifestations *There will be no actual change in the size of the bony skeleton* but the skin may become softer and tissue edema subside The evidences of hyperthyroidism and diabetes may disappear and there will occur a considerable improvement in strength and sense of well being

4 Since the tumor is rarely removed in its entirety symptomatic recurrences may take place Actually of 61 acromegalics operated upon[14] 23 subsequently died as a result of recurrent manifestations of the disease

Combined Surgical and X ray Therapy —It is the general consensus of opinion that surgical removal of a pituitary tumor be it eosinophilic or chromophobic should be followed by intensive radiotherapy [11 14] Such therapy which is directed *towards delaying or inhibiting recurrences* of the tumor growth should be instituted four to eight weeks after the operation and should consist of a full course of irradiation The results of the combined treatment as reported in the literature are somewhat variable Schnitker and his coworkers[81] report no significant difference in the results obtained in 42 patients treated with surgery and x ray in contrast to 33 instances treated with surgery alone On the other hand Henderson[14] reports that 57 per cent of 40 patients treated with surgery alone were free from recurrences at the end of five years while 87 per cent of 31 patients treated with the combined therapy showed no recurrences Grant[1] reports that 70 per cent of the patients treated with surgery and x ray showed a considerable improvement in contrast to 55 per cent treated with surgery alone

Most of the comparative studies in the literature deal predominantly with chromophobe tumors although eosinophilic adenomas are *included* When the data are separated into eosinophilic and chromophobe tumors the former although too few in number from which to draw significant statistical *conclusions* seem to respond better to the combined form of therapy This is not unexpected since the acidophilic tumors are considerably more sensitive to x ray

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Kirklin and Wilder[55] treated 8 patients with acromegaly, 4 males and 4 females, with small doses of estrogenic hormone over a prolonged period of time and reported that "in every instance there was an appreciable clinical change—in some more than in others." Most noticeable was the relief of the headache when present, although improvement in the visual fields, reduction in the basal metabolic rate and an increased sense of strength and well being were also observed. There occurred no change in the character of the bony structure, although, as with the other forms of therapy, the skin became softer and thinner and the soft parts shrank as the underlying edema subsided. These investigators employed Theelin and Amniotin in a dosage of 1000 to 2000 international units administered daily for approximately a month and then on alternate days thereafter for from three months to a year. Subsequently Marrian and Butler[56] showed that estrogens in small doses stimulated, and in large doses inhibited, pituitary activity. Frank[57] pointed out that this effect of the estrogens was particularly directed to the gonadotrophic activity of the adenohypophysis.

It seems well documented, therefore, that estrogens at least are capable of inhibiting adenohypophyseal activity to some degree. Nevertheless, subsequent clinical trials with this form of therapy in acromegaly were not nearly as encouraging as those obtained by Kirklin and Wilder, and the results in general leave a good deal to be desired. In view of the relative innocuousness of the therapy, however, its trial where feasible is desirable. Hamblen[117] recommends the daily oral administration of 5 to 10 mgm. of diethyl stilbestrol given cyclically, that is, for twenty consecutive days of every month starting with the conclusion of the menses if they are present and stopping before the onset of the next bleeding episode.

The Treatment of the Secondary Manifestations of Acromegaly.—The major problems occurring in this group are the treatment of hyperthyroidism, diabetes mellitus, congestive heart failure and the not infrequent evidences of hypopituitarism. A moderate elevation of the basal metabolic rate in the absence of other symptoms of thyrotoxicosis should not be accepted as evidence of hyperthyroidism. Where definite hyperthyroidism is present, however, the forms of therapy available are those which are

normally employed in the treatment of this disease Subtotal thyroidectomy in the acromegalic patient, however is not without a fairly considerable risk Consequently, wherever possible, the use of radioactive iodine or one of the uracil compounds should be used rather than resorting to surgery

The diabetes mellitus occurring in acromegaly is controlled with difficulty unless the primary hyperpituitarism is adequately dealt with Relatively large amounts of insulin and rigid dietary restrictions are necessary for the control of the diabetes Congestive failure occurring in acromegaly is treated exactly as it would be under other circumstances The patient is put to bed at rest if the congestive failure is severe He is digitalized and diuresis is obtained by the frequent use of mercurial diuretics and a salt-free diet with a forced or moderate fluid intake

Eventually, during the course of acromegaly many symptoms of hypopituitarism may develop When the basal metabolic rate is low small doses of thyroid extract may be administered Rarely do such patients require more than a half to one grain of desiccated thyroid extract daily Hypogonadism may be treated with estrogens in the female and testosterone in the male These hormones may be given in generous amounts The acromegalic never develops the frank picture of Addison's disease During the course of acute infections however weakness may become profound and the blood pressure drop to alarming levels Under these circumstances the parenteral use of whole adrenal cortical extract or the synthetic desoxycorticosterone along with an increase in the salt intake is indicated The prolonged or indefinite use of these fractions however should not be encouraged

Summary of the Treatment of Acromegaly —The therapy of acromegaly is directed towards the treatment of the primary disease and the treatment of its secondary manifestations such as hyperthyroidism or diabetes mellitus if present or the treatment of congestive cardiac failure or hypopituitarism The last mentioned is manifested primarily by evidences of hypothyroidism or hypogonadism or both The treatment of these secondary manifestations is essentially the same as it would be were the acromegaly not present although control of the hyperthyroidism or diabetes mellitus would be more difficult

The therapeutic measures available for the treatment of the eosinophilic tumor with its resultant acromegalic manifestations are (1) Hormonal therapy consisting of the daily administration of relatively large amounts of estrogen over a prolonged period of time (2) The use of x ray therapy to the pituitary gland (3) Attempted surgical removal of the eosinophilic adenoma followed by x ray therapy to the pituitary body

The eosinophilic tumors are more sensitive to radiotherapy than are the chromophobe adenomas and consequently a considerable degree of success may be expected with this form of therapy Surgical removal of the tumor should be attempted (1) where loss of vision is threatened (2) in the presence of intractable headache which has not responded to radiotherapy and (3) in the presence of severe and progressive symptoms of acromegaly which have failed to respond to x ray treatment Following the surgical removal of an eosinophilic adenoma the visual symptoms are frequently

dramatically relieved while the headaches are not always alleviated The acromegalic process may be halted and there is some although comparatively slight improvement in the acromegalic manifestations The operative mortality rate is approximately 10 per cent

It is impossible to evaluate adequately the results following the use of hormonal therapy since data concerning this form of treatment are meager The results in general seem to be indifferent although there are one or two reports which are quite encouraging However since this treatment is simple and innocuous there can be no objection to its use alone or in conjunction with radiotherapy where the indications for more radical therapy are not urgent

Illustrative Cases

CASE 1 —The patient was a fifty five year old man whose history of acromegaly dated back approximately twenty years at which time he first noticed a progressive increase in the size of the head and acral parts of the body During the course of the years his hat size had increased from 6¾ to 7⅞ the shoe size from 6½ to 9 while the sleeve length had increased from 32 to 34 inches and he required gloves 4 sizes larger than previously During the past two years he had noticed a marked protrusion of the lower jaw with spreading of the teeth For the past eight years there were recurrent episodes of cardiac palpitation nervousness and tremors and more recently marked sweating and some weight loss He was markedly unstable emotionally with frequent crying spells and prolonged periods of irritability

On physical examination the patient presented typical acromegalic features The head was disproportionately large with marked overgrowth of the facial bones The superior nuchal ridge was prominent and had an underhanging fold of scalp The mandible was massive and protruded so markedly that the lower teeth overrode the upper by a considerable margin The teeth were widely spaced The pinnae of the ears were enlarged and the nose was hypertrophied and prominent There was no exophthalmos or lid lag The thyroid was enlarged to 2 to 3 times the normal size and felt quite irregular The left lobe of the gland was larger than the right The chest was barrel shaped There was a moderate dorsal kyphosis and a considerable sternal bulge The heart was enlarged to the left the rhythm was totally irregular due to the presence of auricular fibrillation and the blood pressure was 130/85 mm of mercury The liver was enlarged Genital examination revealed a moderate penile hypertrophy The testes appeared to be normal The hands and feet were very large particularly the fingers and toes The voice was deep and hoarse and a laryngeal examination revealed hypertrophy of the epiglottis and arytenoids with thickening of the vocal cords There were no abnormal neurologic findings and the visual fields were perfectly normal

The x ray examination of the skull showed a marked enlargement of the sella turcica with moderate decalcification of the calvarium The sinuses were extremely large X ray examination of the hands showed enlargement and decalcification of the bones with coarsening of the trabecular pattern X ray of the chest showed the presence of a substernal thyroid The diameter of the heart was somewhat increased and the aorta showed considerable tortuosity

The basal metabolic rate was plus 28 per cent The peripheral blood count and differential smear were perfectly normal The blood urea nitrogen was 12 mgm per cent sugar 115 phosphorus 5 0 calcium 9 7 cholesterol 220 and cholesterol esters 75 mgm per cent The total proteins of the serum were 6 6 grams per cent of which the albumin was 4 3 and the globulin 2 3 grams per cent A glucose tolerance curve following the administration of 1 75 grams of glucose per kilogram of body weight, was as follows

	mgm per cent
Fasting blood sugar	105
½ hour	160
1	180
2 hours	215
3	180

Following suitable preparation with Lugol's solution the patient was operated upon and a subtotal thyroidectomy performed. During the three-week preoperative preparatory period with iodine the basal metabolic rate fell from plus 28 to plus 16 per cent. There was some slowing of the pulse, a slight gain in weight and perhaps some improvement in the subjective symptoms. Several weeks after operation the basal metabolic rate had fallen to plus 1 per cent but the subjective symptoms were only slightly altered.

Gross examination of the thyroid showed a variable picture. In the left lobe of the thyroid there was a completely encapsulated mass 3.5 cm. in diameter, light yellowish in color and fairly rich in colloid. The remainder of the lobe consisted of closely set cysts well filled with colloid. Here and there cholesterol crystals were seen. A section from the right lobe showed several areas of cystic degeneration each about the size of a dime. There were occasional small nodules rich in colloid. The microscopic examination of the thyroid tissue showed macro- and micro-follicular adenomata with marked cystic changes.

Comment.—This patient represents a fairly classical instance of acromegaly. He demonstrates the long duration and chronic character of the malady, the marked physical abnormality, the evidence of reduced glucose tolerance, the elevated basal metabolic rate, and the symptoms of emotional instability. The x-ray studies of the bones and the skull were characteristic and the marked enlargement of the sella turcica pointed indubitably to the presence of an hypophyseal tumor. The blood chemical findings were normal except for the elevation of the serum inorganic phosphorus which occurs frequently in acromegaly. It is interesting to note that this patient had none of the mechanical symptoms other than an enlarged sella turcica of a pituitary tumor despite the long duration of the disease. There was no headache, impairment of vision, or restriction in the visual fields.

The response to Lugol's solution and the response to subtotal thyroidectomy left a good deal to be desired. There occurred a reduction in the basal metabolic rate but the improvement in the clinical symptoms was comparatively meager. Although this is by no means always true, it happens with great enough frequency in acromegaly so that surgical treatment of the hyperthyroidism when present should be entertained only after the greatest consideration. With the anti-thyroid therapeutic measures available today, such as the use of radioactive iodine and the various uracil compounds, the indications for thyroid surgery in these patients should be limited to those who present pressure symptoms from the mass in the neck or in whom one suspects the possible existence of malignant changes in the thyroid.

Case 2.—The patient was a thirty-six-year-old male whose symptoms dated back twelve years prior to admission to the hospital. At that time it was called to his attention that his facial features were becoming coarse and

thickened. Shortly thereafter he noticed enlargement of his hands and feet. The physical abnormalities became progressively worse, although rather slowly, and during the course of the year he developed the typical acromegalic appearance. Five years after the onset of the illness he began to notice a diminution in vision of the left eye. This rapidly became worse and eventually involved both eyes, and associated with this there was some narrowing of the visual fields. The patient, however, had no headache. He was admitted to a hospital for study, where an enlarged sella turcica was found and a diagnosis of an eosinophilic pituitary tumor made. The patient was given three courses of x-ray treatment to the pituitary over a period of two years, each course consisting of 13 treatments. With this therapy the vision rapidly improved and eventually became perfectly normal. There was, however, no change in the physical appearance of the patient.

The final admission to the hospital occurred two years after the last x-ray treatment. Four days prior to the hospital admission he had contracted an upper respiratory infection. On the morning of admission his temperature had risen to 104 F and he had developed signs of consolidation at the left lower lobe. A pneumococcus type III was isolated in almost pure culture from the sputum. During the course of the next few days he became rapidly worse, developed alarming vascular collapse and died five days after the hospital admission. The only laboratory data available consisted of a white blood cell count of 4000 per cmm, a hemoglobin of 82 per cent and a differential smear which showed 48 per cent segmented polymorphonuclear leukocytes, 29 per cent non-segmented forms, 12 per cent lymphocytes and 11 per cent monocytes. The blood pressure on admission was 160/54 mm of mercury. Shortly prior to death it had fallen to 60/20 mm of mercury.

The postmortem examination revealed a marked splanchnomegaly. The heart was enlarged and weighed 635 grams. All the chambers were hypertrophied, the wall of the right ventricle measuring 1 centimeter at the base while the left ventricle measured 3 centimeters in the analogous position. The trabeculæ were coarse and flattened. The coronary arteries were patent and showed very little atherosclerosis. The liver and spleen were both huge, the former weighing 4,085 grams and the latter 750. The pancreas was large and firm and measured 25 centimeters in length. The kidneys similarly were increased in size. The right kidney weighed 410 grams and the left 380. The cut surface of the kidneys showed a wide cortex. The microscopic examination of the pancreas, liver and kidneys was quite normal except that the glomeruli of the kidneys were very large. The spleen showed extreme congestion such as one often sees during a severe acute infection. The lungs were large and together weighed slightly over 2000 grams. There was extensive consolidation of the left lower lobe. The stomach and intestines were large and distended.

The adrenal glands were only slightly increased in size. On histological examination there was considerable atrophy of the zona glomerulosa. A fairly large amount of thymic tissue was present with enlargement of the Hassal bodies. The testes were normal in size and showed moderate spermatogenesis.

The cut surface of the bodies of 3 lumbar vertebræ presented a rather characteristic appearance with coarse trabeculation and a very dark red succulent marrow. The scalp was thick and the calvarium showed thickening of the occipital and frontal squamæ with complete loss of the normal architecture. The optic chiasm was pushed to the right by a soft yellowish red mass which entered the sella to the left from the stalk of the pituitary. The mass was friable and semi-solid in consistency. The sella turcica was extremely wide and deep, measuring 3 by 4.5 centimeters with a depth of 5 centimeters.

The microscopic examination of the tumor stained with hematoxylin and eosin revealed a fairly uniform cell structure and organization. The cells were either round or pentagonal in outline. Some were loosely arranged while others were packed together tightly. They were usually aggregated around thin walled blood vessels. The cells showed a large central nucleus with abundant cytoplasm which was moderately granular and for the greater part

markedly eosinophilic in staining reaction. An occasional basophil was seen. No mitotic figures were seen and there was no evidence of necrosis. The histologic diagnosis of the tumor was adenoma of the adenohypophysis, predominantly eosinophilic.

Comment.—This patient is of interest from the clinical point of view because of the marked and gratifying response of the progressive visual failure to irradiation therapy of the pituitary. It is important to note that despite the use of enough *x*-ray treatment to cause improvement in vision there was no change in the physical appearance of the patient. The *x*-ray treatment apparently failed to affect the histologic appearance of the tumor and despite careful search there was no evidence of any significant post-irradiation adhesions around the mass. The general splanchnomegaly was most striking in this patient.

The shock-like picture which this patient manifested before death may have been due simply to an overwhelming infection with a virulent organism. It is important to bear in mind, however, that the acromegalic frequently withstands infection poorly and requires the early and generous use of antibiotics where indicated. In addition, at the first sign of impending vascular collapse, whole adrenal cortical extract or the synthetic desoxycorticosterone or cortisone or ACTH should be administered supplemented with adequate amounts of salt.

GIGANTISM

People over 7 feet tall are exceedingly uncommon. Love and Davenport[89] report that in World War I the height limit acceptable for service in the U. S. armed forces was 6 feet 6 inches (198 cm). Among 3¾ million young men between the ages of eighteen and thirty years only 7 cases of gigantism were found. Four of these were acceptable for full army service and therefore were probably not very much taller than the level of 6 feet 6 inches set by the armed services. Thus, of 3¾ million young men at an age period when maximum heights are reached, only 4 were so abnormally tall as to really fall within the category of true giants.

It is by no means clear what constitutes gigantism. Anthropologists have not established any definite height criteria which distinguish between giants and normally tall people. It has been suggested that all persons exceeding 6 feet 10 inches (205 cm.) in height are to be classed as giants.[89] This is, of course, a purely arbitrary classification that has no great claims to scientific validity. But then there are no specific physical criteria that a giant must fulfill. In general, perhaps, the definition suggested by Launois and Roy[30] is most acceptable. They define gigantism as "an anomaly of skeletal growth which leads to a height of the body in excess of the average dimensions of the race and is associated with a characteristic morphological and functional derangement." In this definition giants must fulfill two basic conditions: they must be unusually *tall and their excessive height must be the result of a pathological process*. By far and large this is quite true and it is questionable as to whether any normal men or women ever attain the average height of the true pituitary giant, although there are areas in which overlapping occurs.

It is interesting to observe that there are no great differences in the relative proportions of the various long bones to one another in tall individuals from those in giants. Thus Kaslow and Gray[91] studied the segment proportions in the extremities of these groups. In general in males of normal height the upper arm constitutes 42 per cent, the forearm 33 per cent, and the hand length 25 per cent of the total length of the upper extremity. Women show a slightly different division in that the hand constitutes a somewhat larger fraction of the length of the extremity than it does in men, while in adult negro males the hand is a smaller fraction of the arm than is the case in white males. With an increase in height both in males and females and in the white and colored, there occurs an increase in the forearm and hand fraction and a relative decrease in the percentage size of the upper arm. Essentially the same is true of the 3 segments of the lower extremities.

TABLE 6

PERCENTAGE PROPORTIONS OF UPPER EXTREMITY

	Upper arm	*Forearm*	*Hand*
	White Males		
Normals	42.8	32.5	24.7
Tall Athletes	42.0	33.1	24.9
Giants and Acromegalics	41.6	33.4	25.0
	White Females		
Normals	42.0	32.3	25.7
Giants and Acromegalics	40.4	33.8	25.8

PERCENTAGE PROPORTIONS OF LOWER EXTREMITY

	Thigh	*Shank*	*Foot*
Normal white males	43.0	33.6	23.4
negro males	42.2	35.3	22.5
white females	42.7	34.0	23.3
negro females	42.1	35.4	22.5
Tall males	41.7	35.3	23.0
Giants and Acromegalics	40.8	36.1	23.1

These data would indicate that the segment proportions of giants develop in the same directions as do those of tall individuals, the difference being one of degree rather than of character.

Causes of Gigantism.—There are two major causes of gigantism: (1) hyperfunction of the eosinophilic cells of the adenohypophysis, and (2) primary eunuchoidism. Virilism occurring in preadolescence is generally associated with rapid growth. This entity is commonly due to hyperfunction of the adrenal cortex and much more rarely to hypothalamic disease and to Leydig cell tumors of the testes.[9] Although children with virilizing syndromes, whatever the cause, are tall for their age, they never attain excessive post adolescent heights since union of the epiphyses occurs early.[92] This is in sharp contrast to what is observed in both pituitary and eunuchoid gigantism, where the epiphyses generally fail to unite until quite late. In such cases the epiphyses not infrequently remain open to the age of

markedly eosinophilic in staining reaction. An occasional basophil was seen. No mitotic figures were seen and there was no evidence of necrosis. The histologic diagnosis of the tumor was adenoma of the adenohypophysis, predominantly eosinophilic.

Comment.—This patient is of interest from the clinical point of view because of the marked and gratifying response of the progressive visual failure to irradiation therapy of the pituitary. It is important to note that despite the use of enough x-ray treatment to cause improvement in vision there was no change in the physical appearance of the patient. The x-ray treatment apparently failed to affect the histologic appearance of the tumor and despite careful search there was no evidence of any significant post irradiation adhesions around the mass. The general splanchnomegaly was most striking in this patient.

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GIGANTISM

People over 7 feet tall are exceedingly uncommon. Love and Davenport[88] report that in World War I the height limit acceptable for service in the U. S. armed forces was 6 feet 6 inches (198 cm). Among $3\frac{3}{4}$ million young men between the ages of eighteen and thirty years only 7 cases of gigantism were found. Four of these were acceptable for full army service and therefore were probably not very much taller than the level of 6 feet 6 inches set by the armed services. Thus, of $3\frac{3}{4}$ million young men at an age period when maximum heights are reached, only 4 were so abnormally tall as to really fall within the category of true giants.

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rule these individuals show some of the stigmata of adenohypophyseal overactivity It may be as suggested by Davenport [105] that this subtle and rather modest degree of pituitary overactivity manifested by this group is an inheritable trait



FIG 7 —An 18 year old boy height 218 4 cm (7 feet 2 inches) with markedly enlarged sella turcica Note contrast with physician 177 8 cm (5 feet 10 inches) tall

The data in the literature concerning true giants are relatively scanty and considerably confused This is a disease which because of its dramatic aspects lends itself readily to exaggeration particularly in terms of the heights attained Dr McFarland the curator of the Mutter Museum of the College of Physicians in Philadelphia wrote a most interesting account of this problem [106] In a careful study of the literature he recorded 31 fairly well authenticated instances of true gigantism Of these 28 were males and 3 were females Their heights varied from 7 feet 6 inches (228 6 cm) the Mutter giant to John Middleton who was said to have been 9 feet 3 inches tall (281 9 cm) There were 2 giants Murphy and Middleton reputedly over 9 feet tall 15 over 8 feet tall and 14 giants who varied in height from 7 feet 6 inches (228 6 cm) to 7 feet 10 inches (238 8) The female giants attained comparable heights Thus Marianne Wede it

twenty five and occasionally even to thirty years [94] during which time growth may continue McCullagh[95] states that instances of eunuchoidism have been described in which the epiphyseal lines remained open to the age of forty two years

Eunuchoid gigantism is due to atrophy destruction or surgical removal of the gonads before puberty A common cause is cryptorchidism with atrophy of the testes Such patients are generally quite tall and occasionally they may attain excessive heights approximating those seen in pituitary gigantism Mansbacher[96] describes an instance of a young male of nineteen who was 6 feet 11 inches tall (208 cm) There are in addition other physical evidences of primary hypogonadism such as the failure of the secondary sex characteristics to develop and inadequately developed genitalia The eunuchoid appearance is generally characterized by marked elongation of the upper and lower extremities so that the span frequently exceeds the height by several inches and the sitting height is considerably less than half the standing height of the individual Occasionally eunuchoid gigantism may be familial [96]

True pituitary giants may also manifest hypogonadism In such instances the hypogonadism is secondary to the pituitary disease and is usually due to the pressure of the eosinophilic tumor on the adjacent basophilic cells The essential laboratory difference between primary eunuchoid gigantism and secondary hypogonadism due to pituitary disease is the increase in the urinary excretion of pituitary gonadotropins in the former while in the latter it is reduced The urinary excretion of the neutral 17 ketosteroids may be quite normal or somewhat reduced in both groups of patients Thus, of 46 male eunuchoids in whom the urinary excretion of the 17 neutral ketosteroids was determined and recorded in 25 the results were normal that is above 9 0 mgm per twenty four hours in 20 instances they were below normal and in only 1 instance was there a definite increase in the urinary excretion of the 17 ketosteroids [97, 100, 101, 102, 103, 104] Essentially similar results were obtained in the fewer female eunuchoids reported in the literature

TABLE 7 —NORMAL URINARY GONADOTROPINS IN BOYS AND MEN

(McCullagh [95] according to the method of Klinefelter Albright and Griswold[98])

F S H (follicle stimulating hormone)

Age in years	*mouse units per 24 hours*	
2½ to 12	6 6	13
12 to 15	13	10.5
20 plus	26	10.5

According the Klinefelter Albright and Griswold [98] normal men and women excrete from 6 6 to 53 mouse units per twenty four hour

Pituitary Gigantism —Pituitary gigantism is due to hyperfunction of the eosinophilic cells of the adenohypophysis As in acromegaly this hyperfunction is generally the result of a tumor of these cells less commonly of hyperplasia of the eosinophilic cells and occasionally there is no overt histological evidence of pituitary disease In the last named group a familial history of unusually tall ancestors is almost always obtained and as a

giant were both over 6 feet tall One sibling was normal in size Lest any question arise concerning the pituitary origin of the gigantism in this instance x ray of the sella turcica of the Minneapolis giant showed marked enlargement In addition visual field studies revealed the presence of a bitemporal hemianopsia

In general however pituitary giants are not born of giants and do not propagate giants Schereschewsky[107] records that Piercourt de Saint Quen a French baron created a special fund of several million francs to be devoted to the propagation of giants The venture failed in part because the subject giants were sterile and in part because when they could reproduce their children were generally normal in size

The adult giant is generally not a very strong person despite his enormous size although early in the development of the gigantism his strength may be excessive simply as a result of the tremendous increase in musculature Thus at the age of fourteen the Alton giant had an enormous appetite averaging 6000 to 8000 calories of food daily and was tremendously strong At the age of eighteen he tired easily had inadequately developed musculature was barrel chested and was particularly prone to trophic ulcers and all sorts of indolent infections of the feet Such ulcers and infections are common in giants and are probably due to the lack of pain and temperature sensation below the ankles so often evident in these patients The Minneapolis giant too as an adult was relatively weak tired most easily, and required long periods of sleep The skeleton of the Mutter giant who died probably at the age of twenty two or twenty four years revealed slender curved fragile bones a pigeon breast and a dorsal kyphosis One would suspect that in life he must have been relatively feeble and infirm[106]

The genitalia of the pituitary giant are frequently small and underdeveloped In the case of the Alton giant the external genitalia were small the pubic hair was scanty and both facial and body hirsutism were very meager The Minneapolis giant had an infantile penis and small testes while the prostate could not be felt The distribution of the pubic hair was female in pattern and there was very little facial or axillary hirsutism

The glucose tolerance test is generally normal and the basal metabolic rate somewhat reduced, generally from -15 to -22 per cent A mild hypochromic anemia is often present

Pituitary gigantism is associated with surprisingly few non-endocrine symptoms and signs of a pituitary tumor The sella turcica is generally enlarged but headaches are uncommon and encroachment on the visual fields slight A definite bitemporal hemianopsia occurs infrequently although this was manifested by the Minneapolis giant In general the mechanical signs and symptoms of an intracranial neoplasm are rarely pronounced enough to cause any concern This is in contrast to what is so often observed in the patient with a chromophobe tumor or an eosinophilic tumor causing acromegaly

The prognosis of the pituitary giant is poor They frequently succumb during early adult life generally to some intercurrent infection[114] There are many instances however of survival to middle age The Minneapolis giant when reported by Gray[111] was approximately forty-seven years old

sixteen and one half years of age was said to have been 8 feet 3½ inches (255 cm) tall.[107] It is perhaps desirable to mention that some of the enormous heights recorded have not been on the basis of careful scientific measurements and hence their accuracy is open to some doubt. Humberd,[108] who has devoted a good deal of time and patience in an effort to track down the recorded information concerning the unusual giants, concludes *that none have probably been much more than 8 feet (243.8 cm) tall.* Perhaps the tallest authentic giant was the Alton giant originally reported by Behrens and Barr[109] and subsequently studied by Humberd.[108] The Alton giant at the age of eighteen and one fourth years attained a height of 8 feet 3¼ inches (251 cm).

The association of some acromegalic manifestations with pituitary gigantism is quite common. Such manifestations are present in approximately 40 per cent of the cases[110] and are easily understandable. If hyperfunction of the acidophilic cells of the adenohypophysis occurs before union of the epiphyses takes place then gigantism will result. On the other hand, such hyperfunction occurring in adult life results in the clinical picture of acromegaly. Where hyperfunction starts before epiphyseal union and continues after union takes place, then the patient will manifest both gigantism and acromegaly. *Actually some acromegalic symptoms have been observed in children* with eosinophilic pituitary tumors.[107] In these cases there occurs an increase in the thickness of those bones in which epiphyseal union takes place early. Thus, under normal circumstances an increase in the length of long bones will continue for a considerable period of time after the mandible can no longer increase in length but can in thickness. Exaggeration of this process frequently occurs in young giants, and the characteristic acromegalic manifestations which such patients present are a variable degree of prognathism with wide spacing of the teeth and often an increase in the massiveness of the nose.

Gigantism is a disease which usually begins at puberty and may continue far beyond the period of normal growth.[94] The Minneapolis giant is reputed to have had a second spurt of growth at the age of twenty-eight.[111] Occasionally, however, gigantism may manifest itself at a very early age.[11, 112] Thus the Alton giant, although weighing only 8½ pounds at birth, began to grow rapidly almost immediately.[108, 109] At six months he weighed 30 pounds and at eighteen months 67 pounds. At two years of age his extraordinary size attracted attention. At five years he was 5 feet 4 inches (163 cm) tall, and at nine he measured 6 feet 1 inch (185 cm). From the age of nine to the age of twelve he increased at the rate of 8 inches per year, *from twelve to sixteen* at the rate of 7 inches per year, and from sixteen to eighteen 6 inches per year. When he was a little over eighteen years of age he measured 8 feet and 3¼ inches and weighed 395 pounds.

The family history in pituitary gigantism is generally innocent, although the Minneapolis giant was an exception to this rule. The family history of the Alton giant failed to reveal any unusually tall members during the previous three generations. Three siblings of the patient were normally sized. On the other hand, the paternal grandfather of the Minneapolis giant was the famous Norwegian giant and was reputed to have been 8 feet 4 inches (254 cm) tall. The father and mother of the Minneapolis

progressively more pronounced and by the time he reached the age of eighteen he presented fairly well defined acromegaloid features His nose was large and thick his lower jaw prominent and rather massive His skin was coarse and his hands and feet unduly large and broad even in proportion to his height and weight

On physical examination he was found to be an unusually tall boy well proportioned alert friendly and very intelligent *The fundi were normal the* thyroid was not palpable and the thoracic and abdominal viscera did not appear to be disproportionately enlarged The breasts were those of a normal young adult male There was ample facial axillary and pubic hair sutim the last typically male in distribution The penis and testes were well developed and firm abundant prostatic tissue could be felt on rectal examination The musculature of the extremities and that of the remainder of the body was well developed The neurological examination was essentially negative The cranial nerves were intact the deep reflexes were equal and active and the superficial reflexes were present

The blood pressure was 114 74 The hemoglobin and red blood cell count were normal although the white blood cell count was only 3700 per cmm The differential smear showed a preponderance of lymphocytes constituting 58 per cent and the polymorphonuclear leukocytes constituted 42 per cent of which 2 per cent were nonsegmented forms The basal metabolic rate was −50 per cent on one occasion and −36 per cent on another The glucose tolerance curve following the administration of 1.75 grams of glucose per kilogram of body weight was as follows

	mgm per cent
Fasting blood sugar	74
½ hour after the administration of glucose	104
1	94
2 hours " " "	82
3 " " " " "	62

The serum calcium level was 11 7 mgm per cent and that of phosphorus 3 3 The alkaline phosphatase was 27 King Armstrong unit The blood urea nitrogen was 14 cholesterol 176 and chlorides 527 mgm per cent The serum proteins were 6 7 grams per cent The urine examination was entirely negative and the urinary excretion of the neutral 17 ketosteroids was 14 mgm per twenty four hours which is well within the normal range

The visual fields were perfectly normal and *x* ray examination of the skull showed no enlargement of the sella turcica Roentgen examination of the hands and feet however showed considerable overgrowth of the bones and ununited epiphyses

Intensive *x* ray therapy to the hypophysis was started at the age of fourteen and repeated at intervals for a number of years Between the ages of fourteen and eighteen however he continued to grow and gained 13 9 cm (5½ inches) in height and at the age of eighteen there was still no complete epiphyseal union

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Treatment of Gigantism.—The treatment of gigantism is generally unsatisfactory. This is due in part to the fact that the disease is as a rule not recognized until unusual height has been attained and in part because retardation of the growth process cannot be readily effected with the presently available therapeutic measures. The therapeutic agents available for the treatment of pituitary gigantism are (1) surgical removal of a pituitary tumor if present, (2) the use of pituitary irradiation, and (3) the parenteral administration of testosterone or estrogens.

The indications for the surgical removal of a pituitary tumor are essentially those which apply to acromegaly. Actually, the mechanical signs and symptoms of an intracranial neoplasm are rarely pronounced enough in pituitary gigantism to warrant an attempt at surgical removal. As stated previously, headaches are uncommon and encroachment on the visual fields slight and bitemporal hemianopsia only infrequently occurs. Treatment therefore in general depends upon the prolonged and repeated use of pituitary irradiation as described for acromegaly and the use of testosterone or estrogens. The object of pituitary irradiation is to attempt to reduce the secretory activity of the eosinophilic adenohypophyseal cells while the testosterone is employed in an effort to cause an early union of the epiphyses. The use of the latter agent may cause an initial spurt in growth followed by more rapid epiphyseal closure and subsequent growth retardation. Testosterone may be given either by parenteral injection or by the implantation of pellets. When given by injection, 50 mgm. of testosterone propionate is administered intramuscularly 3 times a week for four weeks and the course repeated at intervals of four to six weeks until epiphyseal closure occurs. Pellets of 150 to 300 mgm. of testosterone may be implanted into the thigh.[116] This is effective for from four to eight weeks and is repeated until the epiphyses unite. In female patients it may perhaps be more desirable to employ estrogens, which have been reported to induce epiphyseal union.[115] Hamblen[117] suggests the daily oral administration of 5 to 10 mgm. of diethylstilbestrol for twenty consecutive days out of every month.

Illustrative Case

The patient is a young male of eighteen years whose present height is 218.4 cm. (7 feet 2 inches) and weight 285 pounds. His family history is essentially negative, his father being 170.1 cm. (5 feet 7 inches) and his mother 165.1 cm. (5 feet 5 inches) tall. He has one sibling, a sister twenty-one years of age, who is 167.6 cm. (5 feet 6 inches) tall. Both the maternal and the paternal grandparents were said to be of modest size. He was delivered normally and weighed 5 pounds 15 ounces at birth. During the first 4 years of his life he developed the usual childhood diseases, including mumps, chicken pox, measles and German measles. Approximately at the age of five he began to show a steady increase *in height in excess of that of other children of his age* and from then on was considerably taller than his friends and schoolmates. At the age of ten he was 171.4 cm. (5 feet 7½ inches) tall, at thirteen 196.8 cm. (6 feet 5½ inches), and at fourteen years of age he was 204.4 cm. (6 feet 8½ inches) tall and weighed 200 lbs. His sexual development was essentially normal. He developed axillary and pubic hirsutism at the age of twelve and facial hirsutism prior to his fourteenth birthday. Penile erections and nocturnal emissions were first noted at the age of thirteen. At the age of fourteen it was observed that his nose was becoming large and his face rather asymmetrical. This became

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pituitary gland showed extensive atrophy and fibrosis. Of the remaining 15 cases, 7 were due to tumor, mostly malignant, 4 were due to cysts, 2 to syphilitic gummas, 1 to tuberculous caseation, and 1 to a hematoma. Occasionally granulomata and more commonly chromophobe adenomas and craniopharyngiomas cause comparatively milder degrees of hypopituitarism. Eosinophilic tumors, as discussed in the previous chapter, are sometimes associated with symptoms suggesting some mild impairment of adenohypophyseal function.

The cause of the atrophic and fibrotic process of the anterior lobe of the pituitary so commonly seen in Simmonds' disease has been attributed for the greater part to postpartum necrosis.[4,5] According to Sheehan and Murdoch[4] such necrosis may follow postpartum hemorrhage. The pituitary undergoes rapid involution at the time of the puerperium with a considerable reduction in blood flow to the gland occurring rather suddenly. If this is further complicated by general vascular collapse due to hemorrhage, the blood flow to the pituitary may be so severely impaired as to cause thrombosis in the vascular sinuses of the gland with resulting infarction and necrosis. The areas of necrosis may vary considerably depending essentially upon the severity of the postpartum hemorrhage and the consequent extent of the thrombosis of the pituitary vascular tree. The infarcted and necrotic areas may be small or large and may even involve almost the entire adenohypophysis. Generally, however, the pars tuberalis and scattered islands of cells just beneath the capsule of the pars glandularis are spared.[5] Healing occurs with fibrous tissue formation and atrophy of the gland, but almost always there remain scattered areas of active tissue, the size of which depends upon the extent of the original necrotic process.

Sheehan's view has gained a good deal of credence during the course of the years. This is due essentially to the fact that in so many instances of Simmonds' cachexia pregnancy occurred just prior to the onset of the disease, and when the question is specifically asked a history of a postpartum hemorrhage associated with that pregnancy can usually be elicited. Thus in an excellent review of 101 pathologically verified instances of Simmonds' disease reported by Escamilla and Lisser[6] pregnancy occurred just before the onset of the disease in 27 of the 67 female cases. In 14 of the 27 patients abnormal postpartum hemorrhage was specifically mentioned. Sheehan and Murdoch[4] demonstrated further that extensive ischemic necrosis of the anterior pituitary lobe is a not uncommon finding in women who die in the puerperium. In 46 instances of women dying fourteen hours or later after delivery, 13 showed such adenohypophyseal necrosis.

In the light of the available data it can be accepted therefore that postpartum hemorrhage plays an important role in the production of those destructive changes in the adenohypophysis which lead subsequently to the development of hypopituitarism. However important this may be as an etiological factor, not all instances of the syndrome can be explained on this basis. In males the disease is often caused by tumors of the pituitary body with resulting pressure atrophy of the adenohypophysis. In Escamilla and Lisser's report[6] 43 per cent showed enlargement of the sella turcica during life, suggesting pituitary growths. The role of infection in

Chapter 4

DISEASES OF THE HYPOPHYSIS (*Cont.*)

HYPOPITUITARISM. SIMMONDS CACHEXIA. PITUITARY DWARFISM

PANHYPOPITUITARISM—HYPOPITUITARISM—SIMMONDS DISEASE OR HYPOPHYSEAL CACHEXIA

HYPOPHYSEAL cachexia is the clinical picture which follows upon the complete or almost complete destruction of the pars glandularis of the adenohypophysis. Although clinicians had been aware of the morbid significance of these clinical manifestations for many years, it was not until the early part of the 20th century that Simmonds[1] suggested that the syndrome was due to destruction of the adenohypophysis. It must be realized, however, that this syndrome represents the extreme phase of hypopituitarism and that there are varying degrees of pituitary injury with more or less corresponding impairment of function. In a general way it may be said that more than 50 per cent of the adenohypophysis must be destroyed before any symptoms ensue.[5] In true hypophyseal cachexia between 95 and 98 per cent of the anterior lobe of the gland is the seat of such a destructive process.

Hypopituitarism may be roughly divided into the following clinical categories:

A. When the disease develops in adults.

1) Hypophyseal cachexia, in which all the functions of the adenohypophysis are gradually and seriously impaired and most of the anterior lobe is destroyed.
2) Acute massive necrosis or infarction of the adenohypophysis in which death occurs promptly and the usual clinical picture of severe hypopituitarism is lacking.
3) Mild to moderate hypopituitarism, in which one or more, but not all, of the adenohypophyseal functions are impaired.

B. When the disease develops in children.

1) Pituitary dwarfism or hypophyseal infantilism associated with gonadal hypoplasia (Lorain-Levi type).
2) Hypophyseal cachexia may rarely occur in children.
3) Dystrophia adiposogenitalis (Frohlich's syndrome). This is more likely a disease of the hypothalamus with some manifestations of hypopituitarism.

Etiology of Hypopituitarism.—The destruction of the anterior lobe is usually due to necrosis, tumor or inflammation. Simmonds' cachexia is most commonly due to postpartum necrosis of the adenohypophysis. In a review on Simmonds' disease published by Silver[33] in 1933, the pituitary pathology was recorded in 41 autopsied cases. In 26 of these patients the

Patients with true Simmonds' disease generally develop weight loss and somewhat less frequently cachexia. But neither weight loss nor cachexia is absolutely essential for the diagnosis. In the group of cases collected from the literature which were verified by autopsy and reported by Escamilla and Lisser[4] the weight loss varied from 8 pounds (3.5 Kg.) to 112 pounds (51 Kg.), with an average of 45 pounds (20.4 Kg.). On the other hand, of 5 patients reported by Williams and Whittenberger[11] none had cachexia although they manifested all the other evidences of Simmonds' disease. Similarly, in 30 patients in whom the diagnosis was verified pathologically and reported upon by Sheehan[5] the nutrition was good in 12, moderate in 7, poor in 3, very poor in 4, and 4 others showed extreme emaciation. In over half of this entire group of cases there was weight loss at some stage of the disease. In general, the degree of weight loss is dependent upon the severity and extensiveness of the adenohypophyseal destruction and the duration of the illness.

TABLE 9.—PERCENTAGE OCCURRENCE OF SIGNS AND SYMPTOMS IN 101 CASES OF SIMMONDS' DISEASE VERIFIED BY AUTOPSY (ESCAMILLA AND LISSER[4])

	per cent
Low basal metabolic rate	90
Asthenia	90
Reduction in gastric acidity	85
Amenorrhea	82
Loss of axillary and pubic hair	80
Abnormal glucose tolerance curve	72
Cachexia	65
Loss of libido and potentia (in males)	55
Dry skin	54
Loss of eyebrows, beard, and thinning of head hair	50
Genital atrophy	49
Pallor	48
Low fasting blood sugar (under 60 mgm. %)	43
Enlargement of sella turcica	43
Decay and loss of teeth	42
Intolerance to cold	41
Hypotension (systolic blood pressure under 90 mm. Hg.)	38
Subnormal body temperature	35
Pigmentation	24
Atrophy of breasts (in females)	23
Bradycardia	21
Hypoglycemic coma	[illegible]

Even more common than weight loss are asthenia, clinical evidences of hypothyroidism, and amenorrhea. Almost all patients with hypopituitarism complain of marked and constant tiredness. The asthenia is perhaps not as profound as that observed in Addison's disease but it is similarly unresponsive to rest. This symptom is probably due to a variety of factors, such as the hypocorticalism, hypothyroidism, the moderate anemia, and anorexia. With improvement in the general condition following substitution therapy of the various glands involved, the asthenia tends to improve considerably. The hypothyroidism may be very pronounced and the basal metabolic rate has been reported to vary from −17 to −51 per cent.[4] The skin is dry, usually coarse, occasionally delicate, and not in

the production of the syndrome is obscure. In 13 per cent, however, the onset of the disease seemed to follow or coincide with a generalized severe acute infection not associated with pregnancy.[6] In a few instances head injuries have been reported as possible etiologic factors, since the disease seemed to follow shortly upon such trauma.[6,7,8,9,10] In these cases fracture of the base of the skull resulted in hemorrhage around the midbrain and pituitary.

Symptoms of Simmonds Disease.—Simmonds' disease is characterized clinically by those symptoms which result from underfunction of the endocrine glands normally regulated by the adenohypophysis. Thus, in the complete picture, the patient will present evidence of hypothyroidism, hyperinsulinism, hypogonadism, and hypocorticalism. In addition there will be a miscellany of symptoms not entirely explained by our present knowledge of the functions of the various endocrine glands but probably representing disturbances in cellular metabolism as part of the general deteriorative process.

Such a complete picture is not always encountered. When the degree of destruction of the adenohypophysis is relatively mild, the clinical manifestations are proportionately limited.

True Simmonds' disease is approximately twice as common in females as in males and may occur at any age, although it is most common between the ages of twenty and sixty years.[6]

TABLE 8.—AGE OF ONSET IN REVIEW OF CASES FROM THE LITERATURE VERIFIED AT AUTOPSY (ESCAMILLA AND LISSER[6])

Age in years	*0–9*	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*
Number of patients	1	8	20	14	22	22	12	0

The symptoms which are ordinarily associated with the disease are (1) weight loss, (2) asthenia, (3) anorexia, (4) amenorrhea in females, (5) loss of libido and potentia in males, (6) intolerance to cold, (7) various psychic manifestations, and (8) occasionally clinical hypoglycemia.

The outstanding physical findings may be (1) cachexia or emaciation, (2) premature senility, (3) loss of axillary and pubic hair, (4) genital atrophy, (5) decay and loss of teeth, (6) dry skin, (7) loss of eyebrows, beard, and thinning of head hair, (8) pallor, (9) atrophy of breasts in females, (10) pigmentation, (11) hypotension, (12) bradycardia, and (13) hypothermia.

The outstanding laboratory abnormalities are usually (1) marked reduction in the basal metabolic rate, (2) reduction in the fasting blood sugar level, (3) abnormalities of the glucose tolerance curve, (4) marked sensitivity to insulin, (5) mild to moderate normochromic anemia, (6) eosinophilia, (7) reduction in gastric acidity, (8) enlargement and destruction of the sella turcica, (9) slight elevation of the serum cholesterol and often (10) a reduction in the serum sodium and elevation of the serum potassium and (11) decrease in the urinary excretion of the neutral 17-ketosteroids and the 11-oxysteroids and the pituitary gonadotropins.

The Adrenal in Simmonds Disease—In extensive destruction of the adenohypophysis one may expect to encounter evidence of adrenal cortical underfunction. At necropsy the adrenals are usually found to be very much reduced in size. There is considerable atrophy of the cortex, the zona glomerulosa and the zona reticularis being particularly thin, although the fasciculate layer is also reduced in size. The cortical lipoids are only moderately decreased. There is rarely any fibrosis of the cortex, and the medulla is generally unaffected except for occasional scarring.[6]

The clinical manifestations of adrenal cortical underfunction are dependent essentially upon the severity of the pituitary destruction and the resultant degree of adrenal cortical atrophy. In general these patients do not present the overt manifestations of Addison's disease, but the presence of underlying adrenal cortical inadequacy may be brought out by various stress measures. Such patients may be precipitated into actual crisis, for example, by the injudicious administration of thyroid extract.[2] Pigmentation occurs in about one quarter of the patients.[6] This pigmentation is similar to that observed in Addison's disease in that it consists of melanin but differs generally in location and intensity. Oral pigmentation, so common in Addison's disease, is unusual in Simmonds disease. Similarly, pigmentation over the knuckles, palmar creases and pressure points is uncommon. In general, when pigmentation is seen in hypopituitarism it consists of a faint brownish discoloration, somewhat splotchy and irregular in appearance, with no particularly striking characteristics as to site.

The serum sodium is frequently, although by no means always, reduced while the serum potassium is often slightly elevated. Of 5 patients with Simmonds cachexia reported by Williams and Whittenberger[11] the serum sodium levels in 4 varied from 127 to 133 milliequivalents per liter. This incidence of reduction in serum sodium level in this illness is greater than that generally reported, however. The response of the patient with Simmonds disease to salt deprivation is similar to that observed in patients with Addison's disease. Thus using the chloride excretion test of Cutler, Power and Wilder, Stephen[13] observed evidence of adrenal cortical insufficiency in 6 of 7 patients with hypopituitarism. Indeed, salt withdrawal may precipitate these patients into characteristic and severe addisonian crisis.

The urinary excretion of the neutral 17 ketosteroids is markedly diminished and generally reduced to less than 1 mgm. in twenty-four hours.[14] In Williams and Whittenberger's group of 5 patients, in 4 the daily urinary excretion of the neutral 17 ketosteroids varied from 0.2 to 1.4 mgm. per twenty-four hours. In 1 patient, a male, it was 2.5 mgm. per twenty-four hours.[11]

The caution observed with regard to patients with Addison's disease must be extended to individuals with Simmonds cachexia. Undue exposure to cold or heat, infections, trauma and excessive thyroid medication may precipitate these patients into adrenal insufficiency. These patients may not be subjected to any surgical procedure, however mild, without suitable preparation and therapy with adrenal cortical extract.

General Pathologic Studies—In addition to the adenohypophyseal destruction and adrenal cortical atrophy already described, the characteristic

frequently there is a brawny non pitting edema of the hands and extremities and puffiness of the face and eyelids. The skin often has a waxy pallor. There is generally a bradycardia, subnormal temperature and hypotension. A systolic blood pressure of under 90 millimeters of mercury is found in over one third of the patients, but occasionally mild hypertension is encountered. The systolic blood pressure in Simmonds' disease generally drops with exertion and changes in posture,[1] but this phenomenon is by no means specific for this illness.

The hair of the head becomes rather scanty, dry and thin and in over half the patients there is a loss of eyebrows. *In almost all patients the* outer half of the eyebrows becomes markedly scanty. The pubic and axillary hair generally disappear and this may occur very early in the disease long before any alarming symptoms manifest themselves. One of the striking features is the tendency of the teeth to decay and fall out. This symptom occurs in somewhat over 40 per cent of the patients[6] and is related to the severity of the illness. An undue sensitivity to cold is a common feature and is probably related to the hypothyroidism. The patients display many psychologic changes. They are apathetic, listless, indifferent, *and forgetful, sometimes confused and disoriented.* Not *infrequently they* become severely depressed, occasionally alternating with excitement.

Amenorrhea is an exceedingly common finding in women with Simmonds' disease and even in milder states of hypopituitarism. Over 80 percent of the women with Simmonds' disease reported by Escamilla and Lisser had amenorrhea, while only 3 of the 32 patients reported by Sheehan failed to show this symptom.[6] As a rule, amenorrhea occurs early in the disease and may be the only evidence of the illness for many years. The amenorrhea is usually not associated with menopausal symptoms, such as hot flashes. There is, however, a loss of libido and in the severe cases a marked atrophy of the uterus and adnexa. The cervix becomes atrophic and the vagina and vulva assume senile characteristics. The breasts may shrink and become devoid of glandular tissue, but more commonly they remain relatively unaltered. Sterility usually follows the onset of the disease but occasionally, in the milder cases, pregnancy has been known to occur.[5,6] If pregnancy can be achieved, it is followed by a marked and permanent improvement in the clinical picture. This is probably due to the hyperplasia and hyperplasia of the remaining adenohypophyseal cells, a process which normally occurs in pregnancy. Of 65 verified cases of Simmonds' disease, 30 or 46 per cent had previous pregnancies, while in over half the onset of the *illness followed the initial pregnancy.* Of *the group of* 30 patients with multiple pregnancies prior to the development of symptoms, in 3 there was one previous pregnancy, in 15 two to five, and in the remaining 12 patients there were more than five previous pregnancies.[6]

Loss of libido and impotence occurred in almost two-thirds of the male patients afflicted. The genitalia become small, the testes and prostate atrophic and spermatogenesis disappears.

Premature senility occurs in almost half the cases. *The patients, particularly* the women, look very much older than their stated years. They appear haggard and worn, despairingly tired and often toothless. The skin is dry and wrinkled, and the scanty hair adds to their aged look.

and capillary blood is withdrawn for sugar determinations twenty, thirty, forty-five, sixty, ninety and one hundred twenty minutes after the insulin injection. In panhypopituitarism there is a normal rate of fall associated with an abnormally slow return to the fasting level, or what Fraser and Smith refer to as "hypoglycemia unresponsiveness".[1] In normal individuals the initial fall may be as marked as in hypopituitarism, but the blood sugar level returns to the normal control values much more rapidly, generally within two hours. The test in hypopituitarism is characterized, therefore, primarily by the failure of the blood sugar level to return to the control value within two hours. The maximum blood sugar fall in both normal individuals and in patients with panhypopituitarism occurs within the first twenty to thirty minutes. In general the depth of the fall is greater in patients with Simmonds' disease than it is in normal individuals, but in dealing with numbers of cases there is considerable overlapping. This test is by no means specific for panhypopituitarism, but may be positive in anorexia nervosa[15] and in Addison's disease. In primary myxedema, according to Fraser and Smith,[15] there is a slow initial fall which may reach a maximum in three-quarters of an hour rather than the usual twenty to thirty minutes. The fall, however, is less marked than that observed in Simmonds' disease and hypoglycemic symptoms frequently do not occur. The return to the control level is often delayed beyond the two hour period, similar to that seen in panhypopituitarism.

The glucose tolerance curve is abnormal in almost two-thirds the patients with Simmonds' disease. Generally the curve is flat, but occasionally it may be diabetic in form. Of 21 verified cases of Simmonds' disease reported by Escamilla and Lisser[6] in whom glucose tolerance tests were performed, 8 were normal, 2 showed a diabetic pattern and in 11 the curve was flat.

As described elsewhere in this chapter the basal metabolic rate is always reduced and in the large series reported by Escamilla and Lisser[6] has varied from −17 to −51 per cent. In most instances the basal metabolic rate varies between −25 and −40 per cent. A diagnosis of panhypopituitarism is untenable in the presence of a normal basal metabolic rate. The blood cholesterol is, as a rule, somewhat elevated, but only occasionally does it attain the marked levels so frequently encountered in patients with primary myxedema. In most instances of hypopituitarism it has varied from 280 to 350 mgm. per cent. The electrocardiographic tracing is similar to that which is generally seen in hypothyroidism. The voltage is low with occasional inversion of the T waves in one or more of the standard leads.

The hemoglobin and red blood cell count are usually reduced. The patients have a moderate normochromic anemia, but rarely severe anemia may be present. Snapper, Groen, Hunter and Witts[16] have reported several instances of hypopituitarism associated with achlorhydria, hyperchromic anemia and subacute combined degeneration. These investigators believed that the course of events terminating in the development of the pernicious anemia was initiated by the hypopituitarism.

The total white blood cell count is either normal or slightly reduced and in most instances varies between 4000 and 6500. There is usually a relative lymphocytosis and in over two-thirds of the patients there is an eosino-

pathologic findings consist of atrophy of the remaining endocrine glands and reduction in size of the thoracic and abdominal viscera. The microsplanchnia may be very striking depending as does most of the clinical and pathologic picture upon the degree of pituitary injury. The thyroid gland is very much reduced in size often to one half or one third of its normal weight. In severe cases the alveoli are scanty and very atrophic with little or no colloid. There is extensive fibrosis and round cell infiltration with numerous lymphoid follicles. Of 29 cases reported by Sheehan with postmortem studies in only 6 were the thyroids normal while in the remaining 23 the degree of atrophy varied from mild to severe with approximately two thirds showing moderate or severe changes.[5] The plasma inorganic iodine is said to be low, generally less than 4 micrograms per cent, while the bioassay of the urine for thyrotropic hormone fails to reveal its presence.[11]

The gonads are very much reduced in size as are the penis and prostate. This is associated with the presence of little or no follicle stimulating hormone in the urine. Thus in 9 patients with panhypopituitarism described by Klinefelter, Albright and Griswold[21] all excreted less than 6.6 m.u. units of follicle stimulating hormone in the urine. In 4 of these patients the pituitary destruction was due to postpartum hemorrhage, and in the remaining 5 patients to pituitary tumor. These authors found the following values for the urinary excretion of follicle stimulating hormone in normal individuals. Males after puberty usually excrete more than 6.6 mouse uterine units daily, up to 53 m.u. units. None excreted as much as 105 m.u. units daily. Females after the onset of the menses and before the climacteric excrete more than 6.6 m.u. units daily and less than 53 m.u. units.

The islets of Langerhans of the pancreas only occasionally show a decrease in size while the parathyroid glands have been described as small in one instance, fatty in another and surrounded by excessive fibrous tissue in a third.[5]

Laboratory Findings in Simmonds Disease.—There is no one specific laboratory determination that is characteristic of Simmonds disease, although there are certain abnormalities that are frequently encountered. The reduction in the daily urinary excretion of the neutral 17 ketosteroids and the 11-oxysteroids as well as of the pituitary gonadotropins have already been described. The former are frequently found to be less than 1.0 mgm. per twenty four hour urine volume, and the latter less than 0.5 mgm. The serum sodium level is generally reduced and the serum potassium level occasionally elevated. The serum sodium is often less than 133 m.eq./l and the serum potassium over 5.0 m.eq./l. The non protein nitrogen and Urea N. of the blood are usually normal except in the presence of adrenal cortical insufficiency when they may be elevated. The serum calcium and phosphorus are normal.

The fasting blood sugar value is generally low and in almost half the cases 60 mgm. per cent or less.[6]

Patients with severe hypopituitarism show a marked sensitivity to insulin as demonstrated by the insulin tolerance test.[15] The test is performed after a twelve hour fast. Two to 3 units of insulin are given intravenously

hypopituitarism. In both illnesses there is a reduction in the urinary excretion of the neutral 17 ketosteroids and of the 11-oxysteroids. In Simmonds disease there is frequently a total absence of these steroids in the urine and almost always a marked reduction while in anorexia nervosa the urinary reduction of these compounds is generally slight or moderate. The eosinophilic response following the injection of 25 mgm of adrenocorticotropin is generally normal in patients with anorexia nervosa and usually inadequate in individuals with Simmond's disease. In those patients who respond adequately to the injection of ACTH, the failure to obtain a reduction in circulating eosinophiles within 4 hours after the subcutaneous administration of 0.3 cc of 1 to 1000 epinephrine would favor the diagnosis of Simmond's disease. In both groups of patients there may be an abnormal response to the insulin tolerance test although this occurs much less commonly in patients with anorexia nervosa.

TABLE 10.—COMPARISON OF SIGNIFICANT SIGNS AND SYMPTOMS BETWEEN SIMMONDS CACHEXIA AND ANOREXIA NERVOSA

Sex	*Simmonds Cachexia* *Female or Male*	*Anorexia Nervosa* *Almost all Female*
History of postpartum hemorrhage	Often present	Absent
Weight loss	May be marked	Always marked
Asthenia	Present	Present
Amenorrhea	Present	Generally present
Loss of axillary and pubic hair	Common	Infrequent
Atrophy of breasts	Common	Rare
Premature senility	Common	Rare
Basal metabolic rate	Low	Low
Fasting blood sugar	Generally reduced	Often reduced
Glucose tolerance curve	May be abnormal	May be abnormal
Insulin tolerance test	Almost always abnormal	Only occasionally abnormal
Serum sodium	Generally reduced	Occasionally slightly reduced
Urinary excretion of 17 ketosteroids	Absent or extremely low	Moderately reduced or normal
Urinary excretion of 11 oxysteroids	Absent or extremely low	Moderately reduced or normal
Eosinophilia	Usually present	Absent
Eosinophilic response to ACTH and epinephrine	Often inadequate	Normal
Salt withdrawal test	Patients often precipitated into addisonian crisis	No effect

Occasionally Simmonds disease may be confused with primary myxedema or with Addison's disease. Careful laboratory and clinical observations can readily distinguish among these conditions.

The Treatment of Simmonds Disease.—The treatment depends primarily upon the degree of anterior pituitary insufficiency. When this is limited with relatively mild clinical manifestations such as oligomenorrhea

philia which may vary from 3 to 40 per cent[5,6] In most instances the eosinophilia varies from 5 to 10 per cent In the light of what we know today concerning the relationship of the eosinophils to adenohypophyseal and adrenal cortical function, this is not astonishing and indeed entirely to be expected

The analysis of the gastric contents generally shows a reduction in the amount of free hydrochloric acid and in about a third of the cases achlorhydria Of 20 instances of Simmonds disease in which the gastric contents were studied only 3 had a normal acidity In 7 there was a reduction in the amount of free hydrochloric acid in another 7 patients achlorhydria and in the remaining 3 instances achylia was present[6]

X ray studies in Simmonds disease are revealing only insofar as they demonstrate roentgen changes in the sella turcica Enlargement and destruction of the sella indicating the presence of a pituitary tumor occurred in 43 per cent of the cases reported by Escamilla and Lisser[6]

The Diagnosis of Simmonds Disease —The diagnosis of hypopituitarism is based upon the presence of a reasonable number of the clinical and laboratory observations described above A history of a postpartum hemorrhage or evidence of an intracranial neoplasm in association with the characteristic symptoms is strongly suggestive of the diagnosis The clinical and laboratory evidence of underfunction of a *number* of endocrine glands in a patient with a suitable history and with the proper symptomatology favors the presence of adenohypophyseal destruction Whenever this diagnosis is entertained it must be remembered that the degree of pituitary destruction varies The easily recognizable hypophyseal cachexia represents almost complete anterior lobe destruction of the hypophysis but there are many instances of less severe pituitary injury with relatively milder clinical manifestations These lesser states are readily recognized if we are aware of the possibility of their existence, and particularly if a history of a postpartum hemorrhage prior to the onset of the symptoms can be elicited

The major stumbling block in the clinical recognition of Simmonds disease is its confusion with anorexia nervosa The latter is apparently not postulated on any primary organic basis It occurs almost exclusively in women generally in young women all of whom manifest serious emotional disturbances In patients with anorexia nervosa there is no history of a postpartum hemorrhage and no alterations in the sella turcica or other evidences of the existence of an intracranial neoplasm This difference in the background or history of the two groups of patients is important although by itself by no means conclusive From the point of view of differences in clinical manifestations the patients with anorexia nervosa only infrequently show the absence of axillary and pubic hair practically never show atrophy of the breasts and most rarely premature senility Eosinophilia so common in Simmonds disease does not occur in anorexia nervosa unless such patients have other diseases associated with eosinophilia There may be some reduction in the serum sodium in both illnesses but it occurs less frequently and is less marked in patients with anorexia nervosa Salt deprivation tests will never induce addisonian crises in individuals with the latter illness but frequently will in patients with severe

Testosterone should be used in all patients with Simmonds disease This is a most effective hormonal agent in the conservation of nitrogen and storing of protein Its use is followed by an increase in strength an improvement in the sense of well being and a gain in weight The dose employed in females should be somewhat less than that given to males and masculinization should be avoided in the former Methyl testosterone may be used in a dosage of 10 mgm 3 times a day by mouth or 50 mgm of testerone propionate intramuscularly 3 times a week Perhaps the most satisfactory method of administration is pellet implantation Males may be implanted with 3 pellets of testosterone each pellet weighing 150 mgm while 1 or 2 pellets will be adequate for females

In addition to the hormonal therapy the patients must receive frequent daily feedings of a high protein high-carbohydrate diet in an effort to prevent hypoglycemic episodes Where the hypopituitarism has been found associated with a pituitary tumor x ray or surgical treatment of the tumor is indicated

Prognosis — The duration of the disease and the outlook is of course dependent upon the extent of the anterior hypophyseal destruction and the underlying cause of the destructive process Where the illness is characterized by minor manifestations dating back to a mild postpartum hemorrhage the duration and relative comfort of life is not affected True Simmonds disease may last for many years Of 90 patients with this illness confirmed by postmortem studies and reported by Escamilla and Lisser[6] the duration of life from the onset of the illness until death varied from five months to forty four years In 20 cases the duration of life was one year or less while in 43 patients it varied from two to ten years and in 23 instances was over ten years In cases of severe acute hypophyseal necrosis or infarction death may ensue within a matter of hours or days after the sudden onset of the symptoms

Death in Simmonds disease is often due to hypoglycemia Occasionally intercurrent infections and disseminated tuberculosis occur terminally The terminal episode is generally one of coma associated with fever leukocytosis and an elevation of the urea nitrogen Hypoglycemia is often but not invariably a cause of the coma Of 52 patients reported by Sheehan[5] 21 died in coma

Illustrative Cases

Case 1 —This is the abstract of a case observed at the Mount Sinai Hospital and previously reported in detail by Silver[3]

The patient was a fifty three year old woman who was perfectly well until the onset of her symptoms at the age of forty Her childhood had been essentially uneventful Her catamenia began at the age of fourteen and were perfectly regular until the beginning of the present illness She had married at the age of twenty and had had 8 pregnancies of which 3 terminated in miscarriages No information regarding the nature of the deliveries and the post partum course of events was available At the age of forty shortly after the birth of her last child her menses ceased With this she noticed that she tired more readily and had great difficulties in doing her usual household work Her weight at this time was 130 pounds (59 kg) which was approximately her usual weight For the next thirteen years until the time of her death she became progressively weaker and more cachectic At the time of the final admission to the hospital she weighed only 60 pounds (27 2 kg) Her teeth had become carious and most of them had fallen out

or amenorrhea or perhaps a moderate reduction in the basal metabolic rate, treatment may be confined to the daily administration of small amounts of thyroid extract or the cyclic use of estrogen or perhaps even the administration of pregnant mare serum in four- to six-week courses at infrequent intervals. Often in these milder instances no therapy need be employed.

The problem of treatment arises in relation to patients with severe hypopituitarism, the cases of so-called true Simmonds disease. In this group therapy is by no means very satisfactory. The ideal form of therapy would consist of the administration of a potent whole anterior pituitary extract capable of stimulating and maintaining those endocrine glands normally controlled by adenohypophyseal secretions. Unfortunately, such a potent extract is not yet available although Sheehan[5] has reported some improvement in 9 patients treated with material commercially obtainable. Most investigators, however, have observed no beneficial effects following the use of presently available whole anterior pituitary extract. Treatment is therefore directed to the control of those signs and symptoms arising from the failure of the various endocrine glands. Since the major manifestations are due to lack of adequate function of the adrenals, thyroid, and gonads, the respective substitutive agents are employed. The treatment of the patient with severe hypopituitarism therefore consists of the administration of whole adrenal cortical extract, desoxycorticosterone, or ACTH or cortisone, thyroid extract, and testosterone. Some caution must be observed when thyroid extract is used either alone or in conjunction with the other endocrine agents. When given alone it produces very little clinical improvement and indeed may occasionally even induce adrenal crisis.[17] This is not particularly surprising since the administration of thyroid extract is frequently associated with some loss of sodium and water.[18] When employed in conjunction with the other agents it is administered in small amounts rarely exceeding ½ grain daily but enough to cause the basal metabolic rate to approach normal levels. In addition, the patient is given either whole adrenal cortical extract or desoxycorticosterone acetate by injection. The dosage of either of these agents is determined by the degree of adrenal cortical impairment. The daily requirement of the desoxycorticosterone acetate will in most instances vary between 1 and 2 mgm. Care must be taken to avoid the development of edema, congestive failure, or hypertension. When a suitable dose has been established, it may be desirable to implant pellets of desoxycorticosterone. If for any reason whole adrenal cortical extract is preferred, it should be administered subcutaneously twice a day and the usual daily requirement would probably vary from 2 to 5 cc. In general, whole adrenal cortical extract is perhaps safer in that the complications of pulmonary edema and hypertension are less likely to ensue, but less economical and somewhat more uncomfortable because of the greater frequency of injections required. Some economy in the use of either the desoxycorticosterone acetate or whole adrenal cortical extract may be effected by increasing the normal daily salt intake. Now that adrenocorticotropic hormone and 17-hydroxy-11-dehydrocorticosterone (Compound E) are more readily available they will probably prove to be a considerable asset in the treatment of Simmonds's disease.

CASE 2 —This case which was originally reported by Fraser and Smith[15] includes certain clinical and laboratory features which are characteristic of the disease but different from the manifestations described by the previous patient

The patient was a woman of thirty who had enjoyed good health up to seven years previously when following a childbirth the symptoms of the present illness began A normal delivery was followed by severe postpartum hemorrhage which necessitated two blood transfusions Since discharge from the hospital she has had amenorrhea a constant tired feeling dyspnea on effort and occasional puffiness of the eyelids and ankles She was almost always depressed tired and listless and had lost all libido Her memory had become increasingly poor and her speech and actions sluggish She was noticeably pale and had become very sensitive to cold

On examination she was fairly well nourished and had lost very little if any weight Her face looked haggard and the skin was dry atrophic and sallow There was no axillary or pubic hair while the hair on the scalp and eyebrows was dry and scanty The teeth were moderately carious The breasts as well as the external genitalia were atrophic and the uterus and adnexa were infantile in size The systolic blood pressure was 90 mm of Hg and the diastolic 72 The patient had a moderately severe hypochromic anemia the hemoglobin being 55 per cent and the red blood cell count 4 2 million per cmm The white blood cell count was normal The x ray of the sella turcica was negative The serum cholesterol was 120 mgms per cent the non protein nitrogen 27 and two fasting blood sugar determinations were 80 and 52 mgms per cent The basal metabolic rate varied between −35 and −45 per cent

An insulin tolerance test was performed and following the intravenous *injection of 5 units of insulin the fasting blood sugar value fell from the control* level of 100 to 40 mgm per cent within thirty minutes and failed to return to the original level within two hours The neutral 17 ketosteroids were entirely absent from the urine on 6 different occasions while the urinary gonadotropin was negative for 5 m u per 100 cc During her stay in the hospital treatment with thyroid extract was started and after six days of such treatment she suddenly developed the clinical picture of an Addisonian crisis with collapse During this episode the serum total base was markedly reduced to 134 milliequivalents per liter while on one occasion the blood sugar level fell to 42 mgm per cent

Comment —In this case the onset could be traced to a postpartum hemorrhage after which her menses ceased permanently although she was only thirty years of age at the time Although the other clinical features were characteristic there was no appreciable weight loss The low basal metabolic rate anemia absence of urinary neutral 17 ketosteroids on several occasions and the failure of the blood sugar value to return to the control level within two hours after the intravenous administration of a small dose of insulin are commonly observed in Simmonds disease It is interesting to note the drop in serum total base and the collapse which followed upon the administration of small doses of thyroid extract

CASE 3 —The case report of Brown and Eder[1] is characteristic of acute necrosis of the anterior lobe of the hypophysis with a rapidly fatal termination

The patient was a forty three year old primipara with hypertension and albuminuria She was delivered by forceps after sixteen hours of labor The patient suddenly went into collapse although only a moderate amount of blood loss had occurred Death followed four days later despite several blood transfusions The temperature rose to 104 F while the systolic blood pressure fell from 184 to 60 mm of Hg At postmortem examination the adenohypophysis contained many areas of frank necrosis

On physical examination she appeared extremely cachectic The skin was sallow and wrinkled and she looked much older than her fifty three years The eyebrows were sparse particularly at the outer margins while the eyes were sunken and the conjunctivæ pale The fundi showed some narrowing of the vessels but otherwise were negative The patient was almost edentulous and the few remaining teeth were carious There was no pigmentation of the mucous membranes and none over the skin The thyroid gland was not palpable the breasts were markedly atrophic while the heart and lungs appeared to be normal The abdominal viscera could not be felt despite the thinness and wasting of the abdominal musculature The pubic hair was sparse as was the axillary hair while the uterus was felt to be small and atrophic and the adnexa could not be felt

The systolic blood pressure was 120 mm of Hg and the diastolic pressure was 80 The hemoglobin was 47 per cent The white blood cell count was 6400 with a fairly normal differential smear The tuberculin test was negative A gastric analysis showed the presence of a complete achlorhydria even after the subcutaneous injection of histamine The stool contained no blood The urine was negative The fasting blood sugar was 90 mgms per cent and the urea nitrogen 14 mgm per cent The basal metabolic rate was −10 per cent Roentgen studies of the sella turcica chest and stomach revealed no abnormalities

Several days after admission to the hospital the patient died suddenly Upon autopsy the major gross anatomical abnormality was a microsplanchnia involving the thoracic and abdominal viscera as well as the endocrine glands The heart was small and weighed 170 grams The right lung weighed 425 grams and the left 340 grams The liver was very much reduced in size but the capsule was smooth and the weight was 895 grams while that of the spleen was 70 grams The kidneys were small and firm each weighing approximately 100 grams The thyroid appeared to be quite normal but the uterus and ovaries were atrophic while the adrenal cortices were definitely thinned although the total weight of each gland was 15 grams which is quite normal The pancreas weighed 70 grams and the pituitary body was definitely reduced in size One other gross finding of interest was the presence of small superficial ulcerations in the lower third of the esophagus and in the small intestine

On histologic examination of the organs there was marked atrophy of the heart with pigmentation fatty infiltration of the liver moderate arteriosclerosis of the kidneys with small areas of fibrosis The ulcerations of the mucosa of the small bowel were superficial and surrounded by a good deal of inflammatory reaction There was considerable atrophy of the thyroid with some fibrosis and some lymphocytic infiltration There was some atrophy of the medulla of the adrenals and a considerable reduction in size of the cortex Microscopic examination of the adenohypophysis showed marked changes There was extensive fibrosis with reduction of the cellular elements and pyknosis of the nuclei The histologic appearance of the adenohypophysis was consistent with that observed in Simmonds disease

Comment —This patient presented the classical clinical features of hypophyseal cachexia The onset apparently occurring directly after the termination of a pregnancy at least suggests the possibility of a *postpartum* episode as the etiologic factor Its beginning with tiredness and amenorrhea was relatively insidious but rather characteristic Cachexia was an outstanding manifestation in this patient During the course of the illness she lost over 50 per cent of her body weight The duration of the illness was approximately thirteen years

The autopsy findings of microsplanchnia with atrophy of the various endocrine glands and the fibrosis and cellular degeneration of the adenohypophysis were characteristic of the disease

grees of malnutrition were given 10 micrograms of crystalline vitamin B_1 orally daily in addition to the usual corrective therapeutic measures such as an adequate diet, rest, iron, liver extract, *etc.*, which they had been receiving for a considerable time before. Following the institution of treatment with vitamin B_{12} there was a marked growth response in 5 of the 11 children. Prior to the administration of the vitamin, there were no clinical evidences of vitamin deficiency in the hair, skin, eyes, mouth or nervous system. After B_1 administration there was a definite increase in appetite as well as increased physical vigor and alertness.

In general, an adequate diet permitting enough protein for tissue building purposes, and enough calories to balance energy expenditure, as well as proper mineral and vitamin supplements, are essential for growth.

Finally, disease of the endocrine glands occurring congenitally or postnatally may play a significant role in growth. Endocrine function not only influences the rate of growth, but by affecting epiphyseal union plays an important determining role in the duration of growth. Androgens, both gonadal and adrenal, influence growth in at least two and perhaps in three ways. The androgens are powerful anabolic factors and thus build tissue and influence growth. On the other hand, they hasten skeletal maturation and closure of the epiphyses. Finally, it is possible that the androgens eventually inhibit the secretion of hypophyseal growth hormone. This is suggested by the fact that very little growth occurs after the onset of sexual maturity. That the absence of androgens does not inhibit growth is evidenced by the fact that eunuchoid individuals are so often tall.

Estrogens exercise a somewhat similar effect to androgens, although to a considerably lesser degree. They hasten skeletal and sexual maturation but produce less marked increases in height than do the androgens. Whereas testicular androgens are probably not secreted before the age of twelve, the ovaries begin to secrete estrogens at about the age of eight years and growth continues for about five years after the onset of the menarche in girls and the development of sexual maturity in boys.[20] Girls with ovarian deficiency are often tall, although those with ovarian agenesis are generally short. In the latter group, however, various other congenital anomalies exist which may determine the short stature.

The role of the adrenal cortical hormones in growth are not entirely clear. In the experimental animal, particularly the rat, bilateral adrenalectomy causes a cessation of growth which can be corrected by the administration of whole adrenal cortical extract.[25] Pituitary homotransplants, on the other hand, which are effective in inducing growth in the hypophysectomized animal, exercise no effect on the bilaterally adrenalectomized one.[6] The growth of boys and girls with Addison's disease is only slightly inhibited and skeletal maturation occurs at the usual time. The carbohydrate fractions of the adrenal cortex cause a breakdown of proteins with conversion to carbohydrates and thus have a catabolic effect. These fractions would therefore theoretically have the effect of inhibiting growth by interfering with the building of tissue. The adrogenic and estrogenic fractions of the adrenal cortex, however, are great tissue builders because of their anabolic actions, but eventually they inhibit growth by causing early union of the epiphyses. The child with adrenal cortical hyperfunction

CASE 4 —A somewhat similar case but complicated by an incompatible blood transfusion with hemoglobin nephrosis was observed on our wards The patient was a young woman of twenty seven who was delivered of a full term baby by a low flap Cesarean section performed at another hospital The patient was a blood type O and RH positive but was transfused by error with type AB blood Twelve hours later she developed a shock like state and during the course of the next two days she became icteric febrile and oliguric She was admitted to the medical wards of the Mt Sinai Hospital for treatment with the artificial kidney On admission to the hospital her temperature was 105 6 F the pulse was 150 per minute and the blood pressure 96/40 The hemoglobin was 34 per cent the red blood cell count 1 73 million per cmm and the white blood cell count varied from 7000 to 16 000 per cmm with some increase in the polymorphonuclear leukocytes The blood urea nitrogen varied from 18 to 65 mgm per cent and the CO combining power was 23 volumes per cent The blood pressure varied from 96/40 to 60/30 The urine output was negligible and prune colored Five days after admission to the hospital the patient died and on postmortem examination the significant findings were complete necrosis of the adenohypophysis and hemoglobin nephrosis

CASE 5 —An instance of acute infarction of the adenohypophysis in a male was described by Kotte and Vonderahe [20]

The patient was a male who had had diabetes mellitus for five years prior to the final illness Two months before his death he developed pulmonary tuberculosis for which he was treated with the usual conservative measures Twenty four hours before admission to the hospital he suddenly developed a temperature of 102 8 F and became semi stuporous On admission the urine sugar was 4 plus but twenty four hours later without any specific therapy sugar was absent from the urine and the blood sugar had fallen first to 31 mgm per cent and several hours later just before death to 20 mgm per cent On autopsy infarction of almost the entire anterior lobe of the hypophysis was found

PITUITARY DWARFISM

General Considerations —Hypopituitarism occurring in children usually results in dwarfism However there are many causes of dwarfism other than destruction with hypofunction of the adenohypophysis

There are 3 major factors which normally determine the growth of an individual These are (1) a genetic factor (2) the nutritional status and (3) the function of certain endocrine glands particularly the hypophysis gonads thyroid and adrenals [2, 3] The genetic factor is more all pervasive than appears at first glance since it determines not only the general capacity of the skeleton to grow but it probably determines constitutional differences in endocrine function among individuals In addition congenital visceral anomalies which may interfere with nutrition are genetically influenced The genetic background of the individual therefore is an important factor in determining the rate and duration of growth There are equally important factors however which may occur post natally Specific visceral disease such as celiac disease chronic renal disease cystic fibrosis of the pancreas acquired as well as congenital heart disease and specific nutritional and vitamin deficiencies interfere with nutrition and may result in marked inhibition of growth

Recently Wetzel and his coworkers [4] reported the dramatic results obtained in 5 of 11 children treated with crystalline vitamin B_{12} administered orally Eleven children from five to twelve years of age with varying de-

Symptoms of Hypophyseal Dwarfism.—The major distinguishing features of hypophyseal dwarfism are (1) a well proportioned diminutive and infantile stature and (2) clinical or laboratory evidences of hypopituitarism. Two additional features *almost* always present are (3) hypogonadism (4) clinical or x-ray evidence of an intracranial neoplasm. The term infantilism so often encountered in clinical endocrinologic literature refers to gonadal hypoplasia associated with dwarfism of whatever cause. Hypophyseal infantilism refers therefore to pituitary dwarfism with hypogonadism. Most pituitary dwarfs manifest infantilism and only very rarely does one mature sexually. Hypophyseal dwarfism with infantilism is frequently referred to as the Lorain-Levi syndrome. During the latter part of the 19th century Lorain and Lineau de la Cour[39] described a group of male and female patients with tuberculosis in whom skeletal and gonadal development was markedly inhibited. There was no clinical evidence of any causative endocrine disease and the defects in the light of our present knowledge could be attributed to chronic infection and malnutrition. More than thirty five years later Levi[39,40,41] described a case of dwarfism with hypogonadism due to a pituitary tumor. Levi's case was an authentic instance of hypophyseal infantilism while those reported by Lorain and Lineau de la Cour referred to infantilism due to entirely different causes—chronic infection and malnutrition although both groups of patients probably looked very much alike. In the endocrinologic literature which has accumulated since the term *Lorain-Levi* syndrome refers to hypophyseal dwarfism with infantilism.

The hypophyseal dwarfs are generally normal in size at birth but early in childhood growth becomes markedly retarded. With this inhibition in growth there usually occurs an arrest in sexual development and not infrequently in the male the testes remain undescended. The epiphyses are ununited and in the infantilistic group remain so indefinitely, while in those few pituitary dwarfs who develop normally sexually epiphyseal union occurs at the proper time. Despite the fact that the epiphyses remain open indefinitely growth may cease early in childhood but in some may continue at an exceedingly slow rate well into the third decade and occasionally into the fourth. Dentition is equally retarded and the temporary teeth may persist to adulthood.

In both males and females pubic and axillary hair is lacking and the voice is high pitched. In the male patients there is no facial hirsutism and penis testes and prostate are hypoplastic. In the females there is pronounced hypoplasia of the ovaries uterus and external genitalia.

Hypophyseal dwarfism is a symmetrical and well proportioned dwarfism. There is a fairly proportionate diminution in the size of the trunks and extremities. The hands and feet are small and delicate the head is tiny and the features childish although as they grow older the skin of the face tends to become atrophic and wrinkled at a relatively early age. The intellect of the hypophyseal dwarf is good but there is considerable emotional lability.

In addition to the endocrinologic signs and symptoms the patients may show clinical evidence of an intracranial neoplasm or cyst such as headaches impairment of vision or encroachment on the visual fields

will grow rapidly so that *for a while he is considerably taller than other* members of his age group When growth finally ceases however he will be short in stature because epiphyseal union occurs so early Finally it is as yet unknown whether the various adrenal cortical fractions specifically influence the growth hormone of the adenohypophysis in any way

Cretinism and hypothyroidism are the most common causes of slow growth or dwarfism in children [3] This would suggest that the thyroid hormone plays some role in growth Still the administration of thyroxine to the hypophyseal dwarf even in the presence of hypothyroidism is without effect The lack of the thyroid hormone in the young results in an inhibition of sexual and skeletal maturation and the cartilage cells show characteristic changes These cells show a swelling and increased staining property over a wide zone so that when bone is eventually formed it is laid down in discrete isolated islets over a wide area resulting in multiple foci of bone formation in the cartilaginous portion of the epiphyses [3] This is in contrast to the solitary focus of bone formation observed in normal individuals Thyroxine will cause rapid acceleration of bone formation in the cretin but not in hypopituitarism Aside from the specific effects just described the lack of the thyroid hormone is associated with a decrease in cardiovascular function impairment of appetite and inhibition of other metabolic functions which interfere with growth

The child with hyperthyroidism is perhaps slightly taller than other members of his age group This effect however may very well be due to the increase in appetite associated with the illness as well as an increase in all metabolic functions

The relation of the adenohypophyseal growth hormone to growth has been discussed in the section on physiology of the adenohypophysis This factor is probably elaborated by the eosinophilic cells of the adenohypophysis since tumor or hyperplasia of these cells result in gigantism or acromegaly The pituitary bodies of congenitally dwarfed mice are completely lacking in eosinophilic cells and no significant amounts of growth promoting factor could be demonstrated in these pituitaries although the presence of adequate amounts of gonad stimulating hormone was found [7, 8]

Human pituitary dwarfism occurs as a result of the destruction of the adenohypophysis Such destruction however results not only in an inhibition of growth but impairment of other important metabolic activities

Etiology of Pituitary Dwarfism —*The destruction of the hypophysis in* dwarfism is generally due to tumor although occasionally a nonspecific atrophy [9] and atrophy due to syphilis[30] and tuberculosis[31] have been reported Friedgood[3] observed a case of hypophyseal dwarfism due to Schuller Christian s disease in which the xanthoma invaded the sella turcica and destroyed the hypophysis

The most common type of intracranial tumors associated with hypophyseal dwarfism are the craniopharyngiomas[33] and to a somewhat lesser extent the chromophobe adenomas Cholesteatomas[34] and teratomas[3] have also been reported, but these are exceedingly rare as a cause of dwarfism There are several instances in which trauma to the skull have been associated with arrested growth but these patients in addition showed evidences of pituitary tumors [36, 37]

with thickening and occlusion of the coronary vessels and frequently myocardial infarcts. Talbot's patient died from a coronary occlusion [44] and one of Gilford's patients died a cardiac death and at autopsy atheromatous plaques were found in the aorta completely blocking the coronary vessel.[46] The adrenals are only infrequently found to be atrophic.[46, 47] In Talbot's patient the adrenals appeared normal both grossly and histologically other than for the sclerosis of the vessels.

The disease occurs in very young children who are apparently perfectly healthy prior to the onset of the illness. The earliest manifestation may begin at one year of age and may be evidenced by a failure to gain weight, slow growth and a falling out of hair. The full blown clinical picture produces a striking similarity of all patients. There is dwarfism, almost complete baldness in both males and females and a marked loss in subcutaneous tissue all over the body. The nose is beaked, the chin markedly retracted and the eyes appear unduly large and prominent probably because of the atrophy of the facial subcutaneous tissue. The ears extend almost at right angles to the head. The skin of the face is thin and tightly drawn. The upper part of the chest is narrow, the abdomen protuberant. There is generally a blotchy, yellowish, faintly brownish discoloration of the skin all over the body, but particularly over the abdomen. The joints of the upper and lower extremities are enlarged, thickened and stiffened. The joints of the fingers and toes are particularly prominent and bulbous. The muscles of the extremities appear wasted and the veins are prominent. The genitalia are usually normal in size and development for the age group. The blood pressure, as a rule, is slightly elevated for the age.

X-ray studies of the skeleton show a normal sella turcica as a rule. The epiphyses at both ends of the humeri as well as the phalangeal, pubic and ischial epiphyses are prematurely united. The neck of the femur may be widened and elongated and may form an almost straight line with the shaft. Several patients have been reported showing considerable demineralization of bone [45, 44] and at least one with multiple fractures.[43]

The basal metabolic rate may be normal, slightly reduced and in several cases elevated. Such increase in basal metabolic rate however is not necessarily due to hyperthyroidism. In the case reported by Talbot [44] the basal metabolic rate was elevated but the serum protein bound iodine was 7 micrograms per cent which is well within the normal range. The appetite in most patients is reported as varying from good to ravenous, despite which weight gain does not occur. The serum sodium, potassium and chlorides are normal[44] and although the serum calcium is generally normal, in one reported instance it was elevated.[40] There may be a mild secondary anemia. The white blood cell count and the differential are usually normal.

Progeria is a slowly progressive and fatal disease and death is generally due either to one of the complications of generalized arteriosclerosis or to an intercurrent infection. There is no specific form of therapy. Talbot's patient was treated with 30 mgms of methyl testosterone daily by mouth and later daily parenteral injections of 25 mgms of testosterone propionate was substituted. On this therapy there followed a gain in weight, some increase in height and some increase in muscular mass, but otherwise there were no significant changes and no improvement in the alopecia. This

These signs of intracranial pressure however rarely become marked enough to invite either surgical or roentgenologic therapy X ray studies of the skull may show evidence of an intracranial neoplasm with encroachment on the hypophysis There may be a deposition of calcium above the sella turcica suggestive of a craniopharyngioma or actual destruction of the sella, although often this part remains infantile or normal in appearance

In addition skull *x* rays will reveal the frontal sinuses to be small and poorly developed the alveolar processes hypoplastic, and the teeth crowded together The body of the sphenoid remains cancellous while the middle table of the skull is hypoplastic The long bones on *x* ray examination are small and slender but fairly well calcified The epiphyses are open and the carpal and metacarpal centers of ossification may be normal or delayed [4]

Laboratory Findings in Hypophyseal Dwarfism —The laboratory findings are those which are commonly seen in hypopituitarism and are characterized by evidence of impairment of many endocrine functions The basal metabolic rate is generally low and as a rule varies from −15 to −35 per cent The fasting blood sugar level may be reduced and there is marked sensitivity to insulin with the production of typical 'hypoglycemia unresponsiveness' following the intravenous injection of 2 units of insulin [15] The serum sodium may be low and there is usually either a total absence or a marked reduction in the urinary excretion both of the neutral 17 ketosteroids and pituitary gonadotropins the latter being less than 6 6 m u units per day [15,21] The serum calcium phosphorus and alkaline phosphatase are normal There is frequently a variable degree of hypochromic anemia but with a normal total white blood cell count and differential Both the systolic and diastolic blood pressures are reduced

Prognosis —The prognosis as to life is primarily dependent on the degree of hypopituitarism present In general these patients are capable of living a normal life span since the degree of hypopituitarism in regard to vital endocrine functions is usually not seriously impaired in contrast to that which occurs in Simmonds disease In 5 casually selected cases of hypophyseal dwarfism from the literature the age at the time of death was sixty-one thirty-eight seventeen ninety one and twenty two years

Differential Diagnosis —Hypophyseal dwarfism must be differentiated from other forms of dwarfism occurring in such states as (1) progeria (2) 'ovarian agenesis (3) cretinism and hypothyroidism (4) primordial dwarfism (5) malnutritive states including chronic renal disease congenital or acquired heart disease celiac disease and cystic fibrosis of the pancreas and finally (6) achondroplasia and rickets

Progeria is a rare childhood disease characterized by dwarfism and premature senility Up to 1940 Mitchell and Goltman[43] collected 13 cases from the literature and added one of their own In 1945 Talbot and his coworkers[44] reported one such patient in detail and mentioned studies being conducted on another The cause of progeria is unknown Most patients reported in the literature had no clinical or pathologic evidence of any hypophyseal involvement Exchaquet[45] suspected that his patient may have had a pituitary neoplasm The patients by far and large do not show any real evidence of hypopituitarism other than the marked cachexia The pathologic studies generally show marked generalized arteriosclerosis

quately resulting in short bones but these bones develop normally Laterally so that they are thick although reduced in size There is a proportionate muscular development and when they mature such individuals often possess great physical strength The upper part of the skull develops normally but the base frequently remains smaller than normal in size due to premature synostosis of the sphenoid and occipital bones As a result of this the face tends to appear somewhat flattened the brow elevated and the bridge of the nose sunken The sexual development of the achondroplastic dwarf usually proceeds normally the epiphyses unite at the orthodox time and in general there is no evidence at present available to indicate any endocrine abnormalities

The dwarfism associated with various *nutritional disturbances* or with *rickets* is readily enough recognized the latter by clinical and roentgenologic evidence of rickets and the former by clinical evidence or a history of malnutrition and clinical evidence of the presence of chronic infection cardiac or renal disease It should be remembered however that prolonged malnutrition may result in impairment of various endocrine functions with a resultant clinical picture that may be confused with primary endocrine disease

Ovarian agenesis is associated with short stature but rarely is there the degree of stunting of growth such as is seen in hypophyseal dwarfism Ovarian agenesis is further differentiated from hypophyseal dwarfism in that in the former there are various congenital anomalies present particularly webbing of the neck In the more adult patients with ovarian agenesis there is generally a marked increase in the urinary excretion of the gonadotropins while the neutral 17 ketosteroids are fairly normal The basal metabolic rate is usually normal or only slightly decreased There is no reduction in the fasting blood sugar level and no impairment in glucose tolerance or increased sensitivity to insulin Clinically the adult patients with ovarian agenesis in addition to various congenital anomalies show hypoplasia of the breasts and genitalia and the presence of some pubic and axillary hair

Dwarfism due to *hypothyroidism* may be difficult to distinguish from hypophyseal dwarfism particularly since the latter so often manifests hypothyroidism Dwarfism associated with cretinism is relatively simple to recognize The coarse hair and skin the thick and protruding tongue the pot belly and retarded mental development readily suggest the diagnosis of cretinism One can often demonstrate the congenital absence of the thyroid in such patients by the administration of a tracer dose of radioactive iodine and show a lack of uptake by passing the Geiger counter over the anterior aspect of the neck The serum cholesterol level in cretinism is high while the serum protein bound iodine is reduced to less than 4 micrograms per cent The difficulty in differential diagnosis arises in dwarfed patients with hypothyroidism who are not cretins In such patients the hair and skin may not be unduly coarse and the reduction in the basal metabolic rate and elevation of serum cholesterol no different from that observed in hypopituitarism The hypothyroid patients however are mentally more retarded than the hypophyseal dwarfs In both instances there is a delay in epiphyseal union and a delay in sexual maturation In hypo

patient died at the age of seven and one half years of a coronary occlusion

The *Primordial* dwarfs differ from the hypophyseal dwarfs in that the former represent essentially endocrinologically normal individuals although markedly stunted in growth They are of good intelligence are born abnormally small in size and growth continues in a slow and inhibited manner They mature sexually at the proper time and the epiphyses unite at the expected age Primordial dwarfs are usually born of normal parents and in turn may give birth to normal children[46] The basal metabolic rate is usually within the normal range while the fasting blood sugar and glucose tolerance curves are normal In the adult primordial dwarfs the urinary gonadtropins as well as the neutral 17 ketosteroids would be expected to be within the normal range

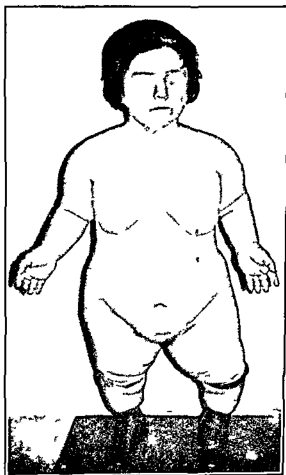


Fig 8 —Achrondroplastic dwarf

The *Achondroplastic* dwarf is a disproportionate dwarf That is there is a disproportionate growth of the trunk and head in contrast to both the upper and lower extremities which are unusually short and often bowed and twisted The epiphyseal cartilages in the extremities proliferate inade

period Where the chorionic gonadotropin exercises no appreciable effect testosterone propionate in a dosage of 25 mgm 3 times a week should be tried The testosterone may be given by mouth in the form of methyl testosterone 10 to 20 mgm daily It is desirable that treatment be started as soon as the diagnosis of dwarfism is definitely established In addition to the various hormonologic agents it is important that the patients receive a nutritious diet with adequate vitamin supplements The importance of these factors in inhibition of growth cannot be overemphasized

In summary then patients with hypophyseal dwarfism should be treated with the following agents (1) Growth principle from the adenohypophysis when it becomes clinically available in an adequately purified and potent form (2) the daily use of thyroid extract (3) the use of chorionic gonadotropin or testosterone (4) an adequately nutritious diet with ample vitamin supplements

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thyroidism, however the lack of sexual development is usually not as pronounced as that observed in hypopituitarism. In hypothyroidism there is marked delay in the appearance and development of the various centers of ossification.[50] This phenomenon, however, is also observed in hypopituitarism, although to a much lesser degree. As previously described the pattern of ossification is quite characteristic in hypothyroidism but this would require biopsy study for demonstration and is therefore hardly a practical method. The therapeutic response to thyroxine may sometimes help in the differentiation. Thyroxine will cause a rapid bone growth in the hypothyroid but not in the patient with hypopituitarism. The urinary 17 ketosteroids and the gonadotropins are reduced in both but the reduction is generally not as marked in hypothyroidism as in hypopituitarism. Both groups of patients are sensitive to insulin and show increased glucose tolerance.

In general the differentiation between the two groups of patients may be difficult and dependent on more subtle clinical observations which will suggest hypothyroidism to the experienced observer. In any event treatment in both conditions should include the use of the thyroid hormone.

Treatment.—Since the distinction between hypothyroid and hypophyseal dwarfism may be difficult and particularly since the latter will usually show some evidence of hypothyroidism both groups of patients should be treated with thyroid extract or thyroxine in addition to whatever other forms of therapy are employed.

The use of the growth principle from the adenohypophysis in the treatment of human hypophyseal dwarfism has so far not yielded any particularly encouraging results. This lack of response may perhaps be due to inadequate dosage or potency of the preparations available or to the possible development of inhibitory factors in the human following its use.[51]

The pure growth fractions have only recently come into experimental use and the clinical data at present available are meager. Edwards, Charles and MacBryde[51] treated and studied 11 patients with hypophyseal dwarfism with pituitary extracts containing growth principle over periods which varied from one to six years. The patients were given parenteral injections of Phyone (Wilson) in increasing graduated doses up to 2 cc. 3 times a week for periods of from two to six months followed and preceded by similar control periods. In only 1 of this group of 11 patients was there a sufficiently marked increase in height to perhaps suggest some specific effect. In any event judgment on the value of the use of anterior pituitary extracts and growth factor in the treatment of hypophyseal dwarfism should be reserved until a greater clinical experience has been achieved.

The use of chorionic gonadotropin and the use of testosterone propionate parenterally or methyl testosterone by mouth have caused considerable increases in height in various types of dwarfism.[3] The use of these agents is particularly indicated in hypophyseal dwarfism since this condition is so often associated with hypogonadism. The chorionic gonadotropin is given parenterally in a dosage of 500 international units 3 times a week for a period of six to eight weeks (9000 to 12 000 international units) followed by a two-month rest period. The periods of treatment are then repeated several times, each period of therapy being followed by a two month rest

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The posterior pituitary control over renal resorption of water is mediated by means of the antidiuretic hormone. That this control is actually hormonal is evidenced by the fact that the isolated denervated kidney is still capable of responding to factors causing secretion of this hormone. Similarly perfusion of the isolated kidney with extracts of the posterior pituitary inhibits water diuresis.[8]

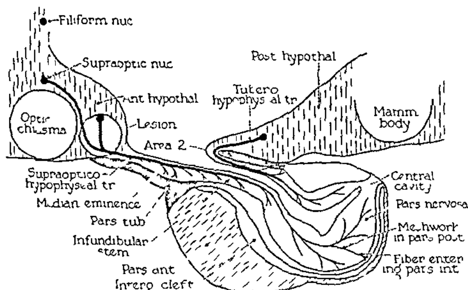


FIG [illegible].—Diagram of a mid sagittal section through the hypothalamus and hypophysis of the cat showing the two divisions of the hypothalamico-hypophyseal tract, the supraoptico-hypophyseal and the tubero-hypophyseal tracts. The broken lines indicate proposed filiform supraoptic connections and the tractus paraventricularis-cinereus of Greving. The obliquely striped circle indicates the position of a typical lesion designed to produce diabetes insipidus. (Ranson, Fisher and Ingram, courtesy of Edwards Bros., Inc.)

Secretion of the antidiuretic fraction by the pars nervosa is conditioned by a number of factors. Perhaps the one of major importance is the osmotic content of the blood[18] and its influence on the receptors lying along the course of the internal carotid artery,[9] particularly in the diencephalon.[10] A rise in the blood concentration of sodium chloride or sucrose, for example, increases the secretion of antidiuretic hormone, whereas other solutes such as urea and glucose are without effect.[9] Exercise, emotion and fainting as well as certain anesthetics and narcotics may increase the secretion of this principle. On the other hand, inhibition of secretion will follow such diverse factors as water ingestion and hypnotic suggestion. The single most important exciter of antidiuretic hormone excretion is dehydration and the most important inhibitor is the ingestion of large amounts of fluids. The various nerve pathways to the pars nervosa indicate routes by which control of secretion of the antidiuretic principle may be influenced.[11] In addition to the supraoptic pars nervosa pathway, fibers from other hypothalamic nuclei terminate in the latter area. These nuclei in turn connect

Chapter 5

DISEASES OF THE HYPOPHYSIS (*Cont*)

POSTERIOR PITUITARY AND HYPOTHALAMIC DISEASE DIABETES INSIPIDUS DYSTROPHIA ADIPOSOGENITALIS (FROHLICH'S SYNDROME) LAURENCE MOON BIEDL SYNDROME

DIABETES INSIPIDUS

DIABETES insipidus is a syndrome which is characterized mainly by the excretion of excessively large quantities of urine and a resultant inordinate thirst The urine which is voided is pale in color of a low specific gravity and the daily volume may be as great as 10 to 20 liters As a consequence of the marked urinary loss of fluids thirst becomes excessive and the patient is continuously involved with the functions of voiding and drinking

The work of Fisher Ingram and Ranson[1] delineated the basic underlying mechanism involved in the production of the syndrome They demonstrated that a supra-optic posterior hypophyseal pathway linking the paraventricular and supra optic nuclei to the pars nervosa of the hypophysis existed A lesion anywhere along this pathway resulted in degeneration in both directions with atrophy and destruction of the nuclei and the posterior hypophysis Lesions of this type which they induced experimentally in the cat with resultant diabetes insipidus have been found repeatedly in human postmortem material in patients with this syndrome However the occurrence of diabetes insipidus is dependent upon the integrity of the adenohypophysis Some observers[2,3] dispute this point and claim that they have produced experimental diabetes insipidus by total hypophysectomy

The pars nervosa normally secretes an antidiuretic hormone This hormone acts upon the distal convoluted tubule to allow adequate resorption of water in order to preserve the proper fluid requirements of the internal milieu of the body

Although antidiuretic principles are elaborated by the posterior pituitaries of all vertebrates only the mammalian kidney is capable of reacting to them Inasmuch as the loop of Henle and the distal tubules first appear in these mammals it is presumed that the renal site of action of the antidiuretic hormone is the distal tubule[4]

It has been demonstrated[5] that 80 per cent of the glomerular filtrate is obligatorily resorbed iso osmotically by the proximal convoluted tubule Hence only 20 per cent of the glomerular filtrate may be selectively subjected to the action of the distal convoluted tubules which explains why in diabetes insipidus the urinary loss cannot reach the level of glomerular filtration

The essential defect in diabetes insipidus is the renal loss of water since nephrectomy abolishes the polyuria and polydipsia and dehydration follows withdrawal of water[6,7]

The posterior pituitary control over renal reabsorption of water is mediated by means of the antidiuretic hormone. That this control is actually hormonal is evidenced by the fact that the isolated denervated kidney is still capable of responding to factors causing secretion of this hormone. Similarly, perfusion of the isolated kidney with extracts of the posterior pituitary inhibits water diuresis.[8]

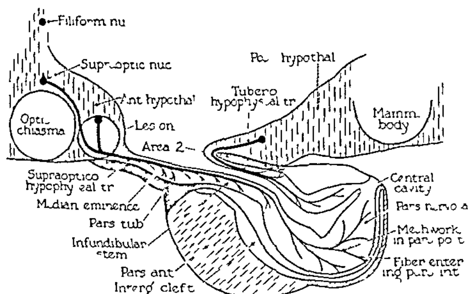


FIG. 9.—Diagram of a midsagittal section through the hypothalamus and hypophysis of the cat showing the two divisions of the hypothalamico-hypophyseal tract, the supraoptico-hypophyseal and the tubero-hypophyseal tracts. The broken lines indicate proposed filiform supraoptic connections and the tractus paraventricularis-cinereus of Greving. The obliquely striped circle indicates the position of a typical lesion designed to produce diabetes insipidus. (Ranson, Fisher and Ingram; courtesy of Edward Bros. Inc.)

Secretion of the antidiuretic fraction by the pars nervosa is conditioned by a number of factors. Perhaps the one of major importance is the osmotic content of the blood[15] and its influence on the receptors lying along the course of the internal carotid artery,[9] particularly in the diencephalon.[10] A rise in the blood concentration of sodium chloride or sucrose, for example, increases the secretion of antidiuretic hormone, whereas other solutes such as urea and glucose are without effect.[9] Exercise, emotion and fainting as well as certain anesthetics and narcotics may increase the secretion of this principle. On the other hand, inhibition of secretion will follow such diverse factors as water ingestion and hypnotic suggestion. The single most important exciter of antidiuretic hormone excretion is dehydration and the most important inhibitor is the ingestion of large amounts of fluids. The various nerve pathways to the pars nervosa indicate routes by which control of secretion of the antidiuretic principle may be influenced.[11] In addition to the supra-optic pars nervosa pathway, fibers from other hypothalamic nuclei terminate in the latter area. These nuclei in turn connect

with subthalamic and thalamic nuclei and thereby with the sensory and motor systems and the cerebral cortex. Finally, sympathetic and parasympathetic fibers are also found in the pars nervosa.

The removal of the antidiuretic principle is followed by certain alterations in renal function. Diodrast excretion is reduced, but this is probably due to altered tubular secretion rather than reduction in renal blood flow.[1] Glomerular filtration is unaltered. The total tubular mass remains unchanged, as do sodium and potassium clearances.[13] The administration of posterior pituitary extract in experimental and clinical diabetes insipidus results in a temporary fall in glomerular filtration and in renal plasma flow with a rise in filtration factor. These effects probably are due to arteriolar constriction.

It is thus apparent that the antidiuretic fraction is intimately concerned with the function of the renal tubular mechanism in the conservation of body water. The extent of this effect varies with the needs of the organism. In addition to this effect on water regulation, the relation of the pars nervosa to sodium and chloride excretion has been the subject of a good deal of study.

At the onset of experimental diabetes insipidus considerable amounts of sodium and chloride are excreted in the urine before equilibrium is established. When posterior pituitary extract is then administered, there is a decrease in the urinary excretion of these electrolytes.[4] Other observers, however, claim that the antidiuretic hormone increases the urinary excretion of chloride. Wallace and his coworkers[14] have found, however, that the effect on chloride excretion may vary. Their results and those of Andlow and his group[15] indicate that the effect of pitressin on the excretion of this electrolyte is influenced by the water load.

The loss of renal concentrating power associated with the defect in tubular resorption of water reflects the inability of the kidney to concentrate its excretory solutes. For this reason, loads with sodium chloride or urea will increase the polyuria, while reduction in the intake of these substances to a minimum will ameliorate the symptoms. Indeed, starvation may induce a relatively normal urinary output.[4]

Following the administration of hypertonic salt solution to the patient or experimental animal with diabetes insipidus, there occurs no change in the ratio of reabsorbed chloride to plasma chloride (R/P), such as is observed under normal circumstances.[16] The explanation for this may lie in the fact that the additional salt may require more fluid for excretion rather than the assumption that an increased amount of salt is resorbed.

From these data it is apparent that the effect of the antidiuretic hormone varies directly with water intake and inversely with salt and urea load. In experimental diabetes insipidus maximal concentration of excreted solutes is not possible, and consequently water loss may in part be dependent upon the amount of such solutes being excreted.

Antidiuretic hormone is destroyed by the liver.[17, 18] It is in part for this reason that edema and ascites may occur in hepatic disease. In these disorders an increased amount of antidiuretic hormone is found in the urine.

From the above consideration it is apparent that the administration of antidiuretic hormone will control the symptoms of diabetes insipidus

However 5 to 15 per cent of such patients[19] are refractory to this form of therapy. The nature of the mechanism involved in such refractoriness has been the subject of a good deal of investigation. Biggart has suggested that in such instances the pathologic process involves the tuber cinereum. It is difficult, however, to conceive how such a lesion could affect the action of exogenously administered hormone. On the other hand, it is more reasonable to assume that such refractoriness represents a failure of the kidney to respond to hormone. Nevertheless, diabetes insipidus secondary to trauma may not be controllable with pitressin. Finally, diabetes insipidus may be induced in the experimental animal by piqure at the bottom of the fourth ventricle, a fact not explainable by our present knowledge.[9]

When there is a defect in the distal renal tubule associated with a failure to respond to antidiuretic hormone, a renal type of diabetes insipidus ensues. Such forms have been reported clinically.[1] In this group, under conditions of adequate hydration, clearances of mannitol, urea, phosphate and para-amino-hippuric acid may be normal, but on reduction of fluid intake these clearances become impaired. At such times water is resorbed to the extent of only 70 to 80 per cent of glomerular filtration, while almost all of the filtered sodium chloride is reabsorbed.

Williams and Henry,[29] investigating a similar group, found normal glomerular filtration, reduced renal plasma flow, an increase in the filtration fraction, a low maximal tubular (Tm) excretion for diodrast, and normal maximal tubular absorption of glucose. The last indicated normal proximal tubular function and the other observations resembled the usual findings in diabetes insipidus.[1]

This syndrome raises the question concerning the possible maturation of renal function in the child.[23] Heller[1] claims that in the infant the distal tubule has not attained its maximal water resorbing power and is relatively insensitive to the antidiuretic hormone. In addition, very little of this hormone is extractable from the neurohypophysis of the young experimental animal. More recent studies,[2] however, are at variance with these findings in that they indicate excellent concentrating power of the kidney of premature infants and a good response to pitressin. These data would suggest that the antidiuretic principle is elaborated at least at birth and the kidney is capable of responding adequately.

There are two other endocrine glands concerned with the action of the antidiuretic hormone, namely, the thyroid and the adrenal.

It has been claimed by Raissotti[6] that thyrotropin is the diuretic principle of the adenohypophysis. Experimentally, thyroidectomy often markedly ameliorates diabetes insipidus, and clinically the onset of myxedema has resulted in a diminution of excessive urinary fluid loss. However, the results of thyroidectomy are inconstant and such a procedure can hardly be advocated for routine therapy of diabetes insipidus. It is possible that the effect of thyroidectomy may be mediated through the reduction of the amount of solute requiring urinary excretion.

The prolonged administration of desoxycorticosterone to experimental animals often results in a diabetes insipidus-like state.[27, 8] In contrast to true diabetes insipidus, however, when the intake of water is diminished the polyuria ceases. The underlying mechanism appears to be a preferen

tial resorption of sodium with respect to water, thus increasing the serum concentration of this electrolyte The characteristic features resulting from bilateral adrenalectomy are a loss of sodium and chloride followed by that of fluid loss When bilateral adrenalectomy is then followed by removal of the pars nervosa death will ensue much earlier because of the superimposed stress of further water loss The rate of loss of electrolytes is no greater, however, than in the simple adrenalectomized animal The greater fluid loss in the adrenalectomized animal with the extirpated pars nervosa results in a relative increase in serum electrolyte values as compared to that which prevails in the animal subjected to adrenalectomy alone Pitressin will not increase the salt loss which follows adrenalectomy Anderson and Murlin[29] have suggested that the facultative reabsorption of water by pitressin must be in progress to allow adrenal cortical extract to regulate the selective renal tubule excretion of sodium and potassium Sartorius and Roberts[30] found that water diuresis produced a fall in sodium excretion and that pitressin produced antidiuresis and an increase in sodium excretion Desoxycorticosterone acetate abolished or modified the effect of pitressin

Etiology of Diabetes Insipidus — The syndrome of diabetes insipidus may be primary or secondary The latter group is the more common and in that group the symptomatology of the diabetes insipidus is part of the over all picture of the underlying disease

Diabetes insipidus may be classified as

1 Primary
    Idiopathic and/or hereditary
2 Secondary (symptomatic)
    a Tumor in or about the supra optic pars nervosa pathway
        Craniopharyngioma
        Pituitary tumors and cysts
        Primary or metastatic neoplasm
    b Inflammatory disease
        Encephalitis
        Measles
        Suppurative meningitis
        Basilar tuberculosis
        Gumma and luetic meningitis
        Actinomycosis
    c Granulomata
        Hand-Schuller Christian disease
        Boeck s sarcoid
        Hodgkin s disease
    d Trauma
        Concussion
        Skull fracture
        Intracranial hemorrhage
        Postoperative
    e Vascular
    f Miscellaneous
        Pellagra

In a review of 160 cases collected from the literature[21,22] tumors of the hypophysis, the hypothalamus, and the posterior cranial fossa accounted for 83 or 52 per cent. Inflammatory diseases such as encephalitis, meningitis, tuberculosis, and syphilis caused diabetes insipidus in 31 instances or 20 per cent, and vascular accidents in 13 or 8 per cent. In 15 instances or 9 per cent trauma to the head was the primary cause of the diabetes insipidus. Five cases or 3 per cent were due to Hand-Schüller-Christian disease and finally in 13 instances the cause was undetermined.

TABLE 11.—CAUSES OF DIABETES INSIPIDUS IN 160 CASES COLLECTED FROM THE LITERATURE

	Number	Per cent
Tumor	83	52
Inflammatory	31	20
Vascular	13	8
Trauma	15	9
Hand-Schüller-Christian disease	5	3
Undetermined	13	8

Warkany and Mitchell[33] in reviewing diabetes insipidus in children found other rarer causes of the disorder such as leukemia, Hodgkin's disease, Boeck's sarcoid, reticulomyco is and pellagra. These illnesses have been found to be the cause of diabetes insipidus in isolated instances in adults as well.

Diabetes insipidus is an uncommon disease. Rowntree[34] found 160 cases in over a million hospital admissions, an incidence of 16 per 100,000.

The age distribution in 53 cases collected from the literature was as follows:

TABLE 12

Age	Number	Per cent
0–10	18	34
10–20	7	13
20–30	8	15
30–40	6	11
40–50	9	17
Over 50	5	10

Both males and females are affected. However, the incidence in males statistically appears to be higher in both the symptomatic and hereditary groups.

The pathology of the secondary group is the pathology of the underlying disease invading or destroying the supra-optic pars nervosa pathway. In the hereditary group only 3 instances have been studied on postmortem examination.[9] In one hypoplasia of the nucleus supra-opticus and nucleus paraventricularis with a reduced number of ganglion cells was noted. The hypophysis and pars tuberalis were reported to be normal. In the second instance there was a paucity of cells in the nucleus supra-opticus and in the nucleus paraventricularis, as well as a marked decrease in the size of the posterior lobe. In the third instance no definite lesion could be proven.

By far the most important type of idiopathic or primary diabetes insipidus is the hereditary variety[47] An excellent review of this group was recently published by Forsmann[20] He found families with sex linked genes for diabetes insipidus as well as family pedigrees with autosomal genes He also noted in one pedigree that pitressin insensitivity existed This fact is of interest in that it is claimed[19] that 5 to 15 per cent of all cases of diabetes insipidus are unresponsive to posterior pituitary extract Biggart found that the tuber cinereum was pathologically involved in these refractory instances but noted the incompatibility of this claim with the known effect of pituitrin on the isolated kidney The mechanism involved in this group is as yet, obscure although the possibility of liver inactivation of the hormone must be borne in mind as well as the probable role of lack of end organ response in the kidney

Such cases of hereditary diabetes insipidus with insensitivity to posterior pituitary extracts apparently the result of end organ unresponsiveness have been reported[35]

Symptoms of Diabetes Insipidus —Diabetes insipidus is characterized primarily by marked thirst and frequency of urination The need for fluids and the urinary urgency are so great as to interfere with work play and sleep The thirst is constant and insatiable However in the presence of an adequate fluid intake per day the clinical condition is bearable If fluid is withheld dehydration and its resultant sequellae are rapid and inevitable These include headache, fatigue muscular pain hypothermia weight loss and tachycardia When the dehydration is marked various psychotic manifestations and cardiovascular collapse may follow

Due to the inability of the kidney to conserve water and concentrate the solutes the urinary specific gravity rarely rises above 1 006 to 1 008 following fluid restriction Terminally however at least in dogs with experimental diabetes insipidus urinary concentrations of 1 016 to 1 018 have been observed[36]

The urinary chloride and urea are low since concentration of these solutes is impaired The chloride concentration is less than the values for plasma It may be noted that whereas under normal circumstances urea and sodium chloride do not compete with each other for water and indeed may utilize the same water for excretion[4] in the patient with diabetes insipidus the urinary volume is proportional to the sum of the molar content of sodium chloride and urea[37] The reduction of fluid intake in the patient with diabetes insipidus will intensify the symptoms On the other hand limitation of the protein and salt content of the diet will ameliorate the clinical picture[37] Indeed Peters[38] has reported a case of marked improvement following starvation resulting from pernicious vomiting of pregnancy

When the fluid intake is unrestricted renal function as measured by clearance studies reveals the glomerular filtration to be normal but plasma renal flow is apparently reduced It should be noted however that the method of measuring this phenomenon may merely indicate inadequate tubular excretion[1] The filtration fraction is elevated while the maximal tubular excretion for diodrast and the maximal tubular absorption of glucose as well as sodium and potassium clearances are all essentially normal With fluid restriction however the clearances become impaired The

serum electrolytes, particularly the chlorides, vary considerably and may be high, low, or normal.

The syndrome of diabetes insipidus resulting from renal end organ insensitivity has been described by several observers. The clinical picture described by Waring and his associates[4] occurs in male children and is familial in distribution. It is characterized by the symptoms of diabetes insipidus associated with dehydration occurring shortly after birth. The fluid loss is generally so marked as to result in fever and constipation. This picture differs from that usually observed in diabetes insipidus in that the former fails to respond to pitressin. Here, too, as in the group discussed above, renal clearances for mannitol, para amino hippuric acid, urea, and phosphate are normal in the hydrated state, but markedly reduced when fluid is withheld. Finally, 70 to 80 per cent of the water filtered is reabsorbed, whereas reabsorption is complete for sodium and chloride.

The Influence of Pregnancy on Diabetes Insipidus.—It is of interest to note that during normal pregnancy there is a relative increase in the urinary volume in the later months. This is of significance, perhaps, in that pregnancy often exacerbates or precipitates diabetes insipidus.

The incidence of pregnancy in patients with symptomatic diabetes insipidus is markedly reduced, due to regressive changes in the genital tract resulting from the debility and damage of the underlying disease. However, in those patients who do become pregnant, there is frequently an intensification of the symptoms in the last two trimesters. In some cases, however, pregnancy does not intensify the disease, and indeed may even ameliorate its course. In hereditary diabetes insipidus, pregnancy as a rule causes an exacerbation of the symptoms.

Forsmann[9] has collected 27 instances of diabetes insipidus which were precipitated by pregnancy. The symptoms usually are noted in the fourth month of gestation, and after partus the diabetes insipidus gravidarum disappears as do the intensified symptoms of permanent diabetes insipidus. *Usually there is a recurrence of the disorder in subsequent pregnancies.*

Diagnosis.—The diagnosis of diabetes insipidus is based upon the clinical history confirmed by tests to establish the basic physiologic defects present. Among the important diagnostic syndromes to be differentiated are diabetes mellitus, chronic glomerulonephritis, and psychogenic polydipsia. *Further helpful confirmatory evidence is the finding of the underlying etiologic basis of the syndrome or a familial or hereditary background and focal or local neurologic or vegetative signs localizing a disease process in the proper portion of the brain.*

The most important criteria are the excretion of a daily urinary volume *exceeding four liters and a fluid intake in excess of 5000 cc.* These criteria are really arbitrary, and it is possible that the volumes may be less in true cases. The specific gravity usually does not exceed 1.006 to 1.008 except terminally. This may be tested by fluid deprivation for twelve to sixteen hours, as in the standard concentration test for renal function. Care must be taken, however, *that dehydration is not allowed to progress too far.*

A response to pitressin is of confirmatory value but does not rule out psychogenic polydipsia. However, it should be remembered that 5 to 15

per cent of true instances of diabetes insipidus fail to respond to posterior pituitary preparations

A further test of the ability of the posterior pituitary to secrete an antidiuretic hormone is provided by the test devised by Carter and Robbins[39] based on the studies reported by Hare and his coworkers[16 40] This test is of great value in differentiating true diabetes insipidus from psychogenic polydipsia It is based on the observation that the administration of hypertonic saline will inhibit a water induced diuresis in the normal individual but not in a patient with diabetes insipidus

The test is performed as follows *All* antidiuretic therapy is stopped in order to permit a recurrence of symptoms Fluid is withheld for eight hours prior to the onset of the test Food however is permitted The patient is hydrated by the oral administration of 20 cc of water per kilo of body weight over a period of one hour Thirty minutes later a catheter is inserted and urine is collected in fifteen minute periods and recorded as cc of urine flow per minute After two control fifteen minute periods provided the urine flow exceeds 5 cc per minute 2 5 per cent sodium chloride is given intravenously at the rate of 0 25 cc per kilo per minute for forty five minutes If no decrease in urine flow ensues during the infusion or in 2 fifteen minute periods thereafter 0 1 unit of pitressin is then injected intravenously and the effect observed In this way if no inhibition of water diuresis by saline is noted the responsiveness to pitressin is demonstrated in order to prove that posterior pituitary hormone has not been secreted In normal individuals and in patients with hysterical polydipsia there occurs a decrease in the urinary volume during and following the administration of hypertonic saline This is in contrast to that which is observed in patients with diabetes insipidus

Diabetes mellitus is readily ruled out by the absence of glycosuria and hyperglycemia However both diabetes mellitus and diabetes insipidus may be present in the same patient as occurred in a member of our series In such instances the glycosuria and hyperglycemia will disappear with the administration of insulin, but the underlying diabetes insipidus will persist

Chronic glomerulonephritis may be differentiated by the clinical history hypertension albuminuria the finding of casts and/or red cells in the urine and in the late stages of a specific gravity fixed at 1 010 In these patients the power of dilution as well as of concentration is lost

Treatment —The treatment of diabetes insipidus consists primarily of the administration of the antidiuretic hormone This may be given in one of several forms depending upon which products are available The two most useful forms of medication are dried pituitary powder used by nasal insufflation and pitressin in oil for parenteral use[49]

Posterior pituitary powder may be used for intranasal insufflation either as a snuff or by means of a spray[50] Its advantages reside in the ease of application its inexpensiveness and the relatively small dose necessary It is nonirritant in most instances to the nasal mucosa Its effect is rapid and its duration of effectiveness is for three to four hours It is much less useful in the presence of any acute or chronic inflammation of the nasal mucous membrane If used as a snuff a pinch of 50 mgm may be taken every three to four hours or if a spray is used (DeVilbiss #4) even smaller quan

tities may be effective[41] Other intranasal forms of medication such as the use of aqueous pitressin solution (0 5 cc 3 times a day) as a spray or jelly, or pitressin or pituitrin applied by nasal pledgets although useful are not as convenient nor as satisfactory

Pitressin tannate in oil (5 pressor units per cc) is administered subcutaneously or intramuscularly, but never intravenously The advantage of this form of therapy is the prolonged slow absorption of the hormone and consequent prolonged antidiuretic effect It may be given in a dosage of 1 cc every thirty to eighty hours and proper adjustments made for the individual case[4, 43, 44]

Aqueous pitressin (20 pressor units per cc) is effective but has the disadvantage of necessitating several injections a day if employed parenterally since its effect is quite transient It is therefore much less useful than pitressin in-oil and has for the most part been replaced by the latter drug in the treatment of diabetes insipidus Aqueous pitressin when employed is given in doses of 0 5 to 1 0 cc or more every four to eight hours

Obstetrical pituitrin and surgical pituitrin (which is twice the strength of obstetrical pituitrin) contain both the pressor and oxytocic principles They may be used in 0 5 to 1 0 cc doses as necessary but they are not as useful as pitressin because of the side effects of the oxytocin

Pellet implantation would constitute an ideal form of therapy, since this method can elicit a therapeutic response However the usefulness of this measure is limited by the irritating and inflammatory reaction which is set up in the tissues[45]

Due caution must be paid to the toxic effects of posterior pituitary extracts Most important, of course is the development of water intoxication when large amounts of water are habitually drunk after the start of specific therapy Patients may develop confusion improper coordination nausea and vomiting lowering of the body temperature headache and even convulsions and death Hypertonic salt solution will overcome the hypotonicity of the internal environment, and diuretics will then remove the excessive fluid and salt

Diet is an important adjuvant in treatment A salt free diet reduces polyuria In addition a low protein diet will further result in a decrease in the solutes in the urine requiring excretion and thereby aid in reducing the water exchange The use of aminopyrine[46] has been suggested in the treatment of diabetes insipidus, particularly in those instances which are unresponsive to pitressin The results however are variable and the drug can hardly be relied upon for the symptomatic control of the disease When employed it is used in the dosage of 1 gram 3 or 4 times a day

Specific attention to the etiologic causes of the syndrome are always important Surgical intervention x ray therapy and antibiotics must be employed when the indication for their use exists

Thyroidectomy *per se* for the treatment of diabetes insipidus is not warranted at present As mentioned elsewhere in this chapter (p 143) both experimental and clinical diabetes insipidus may be relieved in great measure by thyroidectomy or the development of myxedema It is believed by some that the diuretic effect of thyroid hormone or its production as the result of release of thyrotropic hormone is part of the mechanism for

the polyuria in diabetes insipidus However the clinical results are such that thyroidectomy is not warranted for diabetes insipidus alone but only where indications of disease of the thyroid exist It might be desirable to employ an antithyroid drug such as propyl thiouracil to evaluate the role of hypothyroidism as a therapeutic measure particularly in those patients unresponsive to other forms of therapy

Prognosis —In hereditary diabetes insipidus there is no effect on longevity resistance to infection or health In symptomatic diabetes insipidus the prognosis is based upon the underlying disease In general spontaneous recovery may occur when the disease is caused by trauma or infections or when it appears for the first time during pregnancy

Illustrative Cases

CASE 1 —A forty-eight year old man was admitted to the medical wards of the Mount Sinai Hospital complaining of weakness weight loss bitemporal and frontal headache anorexia and loss of libido of two years duration For the past nine years he had had severe polyuria and polydipsia and had been drinking 5 to 6 gallons of water a day

The pertinent findings on physical examination included bilateral blurring of the optic discs slight hepatomegaly and a blood pressure of 180 mm of mercury systolic and 110 diastolic There were xanthomatous infiltrations in the eyelids of both eyes

The laboratory studies failed to reveal any urinary abnormalities other than a maximum concentrating power of 1 008 The hemoglobin was 58 per cent The red blood cell count was 4 79 million per cubic millimeter The white blood cell count and differential were essentially normal The basal metabolic rate was 10 per cent The blood urea nitrogen was 47 mgm per cent The blood cholesterol was 210 mgm per cent of which the esters were 90 mgm per cent X ray of the skull showed a normal sella turcica with no evidence of any destructive process involving the skull

While in the hospital his total fluid intake during a twenty four period was often approximately 2300 cc and the maximal urinary volume was roughly 5 liters

Five months later he was readmitted to the hospital complaining of headache impaired vision further weakness and weight loss pain in the chest and left arm dyspnea and orthopnea

The physical examination at this time revealed the blood pressure to be slightly higher The fundal examination showed characteristic evidence of a hypertensive retinopathy with papilledema The heart was slightly enlarged A friction rub was audible over the right chest

Roentgen studies of the chest showed numerous linear strands the etiology of which was not apparent X ray of the humerus revealed an irregular density of the neck and mottling of the shaft This together with a destructive lesion of the fifth right rib suggested the possibility of metastatic malignancy or Hand-Schuller Christian disease

The *cardiac failure increased while the blood urea nitrogen rose to 97 mgm* per cent and the patient died in pulmonary edema following a convulsive episode

At postmortem examination a diffuse lipoid granulomatosis characteristic of Hand Schuller Christian disease was found which involved most of the bones and viscera *Granulomatous lesions were found at the base of the brain* surrounding but not involving the posterior lobe of the hypophysis

Comment —Diabetes insipidus in this instance was due to Hand-Schuller Christian disease in which the granulomatous lesions involved the mid brain while the posterior lobe of the hypophysis was essentially intact

Hypertension and renal failure are not directly associated with diabetes insipidus In this patient these findings were due to a ureteral obstructive nephropathy resulting from local deposits of granulomatous tissue

CASE 2 —A thirty six year old man was admitted to the hospital with complaints of excessive thirst and polyuria Twelve years previously he had sustained a severe head injury, necessitating a craniotomy for a depressed fracture and a subdural hematoma Seven years after the accident he noted the onset of polyuria and polydipsia He had been studied in several hospitals for these complaints A diagnosis of diabetes insipidus had been made and following the administration of pituitrin these symptoms subsided He had tried various modes of administration of the antidiuretic factor and entered the hospital for determination of the type of preparation and mode of administration best suited for him

The physical examination revealed the scar of a depressed fracture over the left side of the head There were paralyses of the right internal external and inferior recti muscles amaurosis of the right eye a right lower and left upper facial paresis deviation of the jaw to the left depressed reflexes and light weakness of the right upper and lower extremities

When the administration of pituitrin was discontinued there resulted a marked increase in the daily fluid intake which often reached 14 liters This was associated with a urinary output of 12 liters Pyramidon in the amount of 25 to 30 grams a day was without influence on the fluid exchange

After trials with various forms of therapy it was found that the symptoms were most effectively relieved in this patient with the subcutaneous administration of aqueous pituitrin

Comment —This case is of interest in that it presumably represents an instance of diabetes insipidus following upon a head injury In this patient approximately seven years elapsed between the time that the head injury was sustained and the onset of the symptoms Careful investigation failed to reveal any other cause for the diabetes insipidus It is interesting to note that pyramidon exercised no effect on either the polyuria or the polydipsia while nasal pituitrin was much less effective than the subcutaneous administration of aqueous pituitrin It is important to remember however that this represents an individual variation Generally the response to intranasally administered pituitrin is effective and satisfactory

CASE 3 —A fifty two year old woman complaining of marked thirst of nine months duration was admitted to the hospital At the time of the onset of the symptoms glycosuria and hyperglycemia were noted On a suitable dietary regimen the glycosuria disappeared She neglected the diet however and seven weeks prior to admission to the hospital polyuria and polydipsia again appeared

The physical examination was essentially negative The laboratory examination revealed a diabetic glucose tolerance curve The sedimentation rate was normal The hemoglobin and peripheral white and red cell counts as well as the differential were essentially normal The maximal urinary specific gravity was 1014 X ray of the skull failed to reveal any abnormalities The visual fields were normal

Over a period of three weeks her fluid intake and output varied from 2 to 5 liters per day Inasmuch as the glycosuria was minimal it was suspected that the excessive fluid exchange was due to diabetes insipidus although no focal neurological etiology could be established The polyuria and the polydipsia were completely controlled following the parenteral administration of pitressin and the intranasal insufflation of posterior pituitary powder She was therefore discharged for further observation

Four months later she was readmitted because of failing vision At this time a partial bitemporal hemianopsia was noted A spinal fluid examination showed an increase in the protein content to 120 mgm per cent, but no other spinal fluid abnormalities were found The electroencephalogram revealed an abnormal pattern Pneumoencephalographic studies showed the presence of a lesion in the anterior portion of the third ventricle

Subsequent study demonstrated the presence of fluid in the right pleural cavity Carcinomatous cells were found in the fluid removed for pathologic examination

Three weeks later the patient died

Comment —Two points are of interest in this case The first is that this patient demonstrated the presence of both diabetes insipidus and diabetes mellitus The diagnosis of the former was suspected because the volume of the fluid intake and urinary output were out of proportion to the relatively mild hyperglycemia and glycosuria and because the response to pitressin was so prompt and marked

The second point of interest is the relation of diabetes insipidus to an intracranial metastatic lesion secondary to a primary pulmonary malignant process It should perhaps be emphasized that primary pulmonary malignancy with intracranial metastases as a cause of diabetes insipidus is not uncommon This case further emphasizes that diabetes insipidus may often be secondary to a more significant underlying process

FROHLICH'S SYNDROME (ADIPOSOGENITAL DYSTROPHY)

In 1901 Frohlich[15] reported the case of a boy of fourteen who had been complaining of severe headaches some vomiting, rapid weight gain and progressive diminution in visual acuity with complete blindness in the left eye On physical examination he was rather obese and somewhat short in stature There was enlargement of the breasts The testes appeared to be small while the penis was normally developed although deeply embedded in fat tissue There was no axillary hair and only occasional pubic hair It was very evident that the boy had an intracranial tumor and at operation a tumor probably a craniopharyngioma, was found the cystic contents of which were evacuated

A year previously in 1900, Babinski[3] published a report on a follow up study of the case of a young woman originally described by Manoff This patient had a tumor of the pituitary with hypogonadism

These two reports served as a basis for the subsequent development of the concept of Frohlich's syndrome In 1904 Erdheim[54] suggested that the obesity observed in Frohlich's syndrome was due to "injury or stimulation on the region of the base of the brain This set the stage for a controversy which has ensued to this very day concerning the respective roles of the adenohypophysis and the hypothalamus in obesity and in the development of Frohlich's syndrome It is clear on the basis of the experimental evidence available that the hypothalamus plays a significant and probably primary role in certain types of obesity[55,56,57] The fact that adiposogenital dystrophy has been observed to occur in individuals with hypothalamic tumors and in various inflammatory lesions of the base of the brain in which the

pituitary is not involved would strongly suggest that this syndrome is due primarily to hypothalamic disease. The question as to whether the hypogonadism is due to hypothalamic disturbance alone or to the influence of the latter on the secretion of gonadotropic factors by the pituitary is at present a moot point.[5, 76] The fact remains that postpubertal Frohlich's syndrome can occur in the absence of any overt adenohypophyseal disease but in the presence of hypothalamic injury and associated with this there is a considerable reduction in or even total absence of urinary gonadotropins.

The modern experimental studies concerning the role of the pituitary and of the hypothalamus in the production of obesity began with the work of Crowe, Cushing and Homans.[57] These investigators produced the adiposogenital syndrome in dogs by hypophysectomy and by hypophyseal stalk interruption. In the light of our present knowledge it would appear reasonable that these early attempts at experimental hypophysectomy and hypophyseal operations would be attended by not inconsiderable injury to the hypothalamus. The first significant experimental evidence involving the hypothalamus was provided by the studies of Camus and Roussy,[5] who produced a similar syndrome by puncture of the hypothalamus. In 1921 Bailey and Bremer[59] in careful experimental studies in the dog demonstrated conclusively that the adiposogenital syndrome could be produced by primary hypothalamic lesions. Several years later Smith[60] working with rats was able to remove the hypophysis completely without doing damage to the hypothalamus. In young animals subjected to this procedure growth and genital development were impaired but there was little or no tendency to develop obesity. In another set of animals this investigator produced injury to the hypothalamus with chromic acid without affecting the hypophysis with resulting adiposity and genital dystrophy. Grafe and Grunthal[61] obtained similar results in dogs following injury in the tuberal region. Finally Hetherington and Ranson,[6, 63, 64] employing the Horsley Clarke stereotoxic instrument with which isolated electrolytic lesions may be produced in various locations within the brain stem, established beyond question the role of the hypothalamus in the production of obesity. They showed that obesity regularly followed the production of lesions restricted to the hypothalamus and that such obesity was produced regardless of whether the adenohypophysis was present or had been surgically removed and also that no amount of pituitary damage could induce obesity in the presence of an intact hypothalamus.[65, 66] These investigators further demonstrated that not all lesions of the hypothalamus result in obesity. They found that large lesions of the anterior or dorsal hypothalamic areas or of the suprachiasmatic and preoptic regions failed to evoke obesity, while the most positive results were obtained when injury was produced in the ventromedial nuclei or in areas ventrolateral to these nuclei. Somewhat less pronounced obesity occurred when injury was induced in the tuberal or posterior levels of the hypothalamus.

The obesity observed following experimentally induced hypothalamic lesions arises primarily from a marked increase in food consumption, to a lesser extent associated with a decrease in locomotor activity.[63] The enhanced appetite observed after hypothalamic injury was first suggested by Keller and his colleagues[67] and has since been adequately confirmed[68, 69, 70]

Etiology. — The syndrome is associated with inflammatory disease of the midbrain as well as with tumors of the hypothalamus and adenohypophysis. One must assume that *pituitary tumors produce the syndrome by pressure on the midbrain*. The inflammatory lesions that have been described in association with Frohlich's syndrome are encephalitis and meningoencephalitis with resulting postencephalitic adiposogenital dystrophy, tuberculosis with tuberculoma formation in the midbrain, syphilis and chronic abscess. The most common brain tumors associated with this syndrome are craniopharyngiomas, although chromophobe adenomas, meningiomas, midbrain gliomas and cholesteatomas have been described.[71]

Clinical Manifestations. — The clinical concept of Frohlich's syndrome has been very much abused over the course of the years. The eponym was used loosely and was lightly applied to boys and girls who were obese and in whom sexual maturation was relatively slow. Our present knowledge of the various gonadal dystrophies still leaves a good deal to be desired, but in perusing the literature dealing with the reported instances of Frohlich's syndrome it is evident that included in the category are cases of *Klinefelter's syndrome, nonspecific obesity, primary diffuse hypogonadism* and obesity associated with delayed sexual development. For purposes of clarity and clinical accuracy the diagnosis of Frohlich's syndrome must be reserved for those individuals who manifest a curiously distributed obesity, hypogonadism, absence or reduction of urinary gonadotropins and clinical evidence of intracranial disease. In preadolescent boys and girls the diagnosis can be sustained only if sexual maturation fails to occur, since hypogonadism is the normal state prepuberally.

The disease may have its onset before or after puberty and in adult life. When it occurs before puberty it is characterized by obesity which involves particularly the neck, chin, hips and upper part of the thighs. The breasts are usually enlarged in boys, and the upper and lower extremities are rounded, with long tapering fingers and toes. Associated with this obesity are poorly developed testes and a penis which appears smaller than it is since it is embedded in fat. The skeletal defects consist mostly of failure of the epiphyses to unite and of shortness of stature. There is generally evidence of intracranial disease. This may be manifested by the clinical symptoms of hypothalamic disease such as polydipsia, polyuria and hypothermia, or there may be neurological signs suggestive of an intracranial process. *Finally, where the syndrome is due to hypothalamic or hypophyseal tumors* there may be encroachment on the visual fields, fundal changes or roentgenologic evidences of ballooning or destruction of the sella turcica. In female children the picture is characterized mostly by obesity and evidence of some *pathological intracranial process*. *In adult males the disease* is characterized by the type of obesity already described and by definite hypogonadism with loss of axillary, pubic and facial hair. In adult females there is obesity and amenorrhea, and in both sexes a reduction in, or absence of, urinary gonadotropins.[7] *In adults, as in children, evidence of* intracranial disease can usually be elicited.

Adiposogenital dystrophy must be differentiated from primary gonadal disease and from instances of obesity with delayed sexual maturation.[73,74] Primary gonadal disease may be associated with obesity which is *indis-*

tinguishable from that observed in adiposogenital dystrophy. Klinefelter's syndrome, which is a more highly selective gonadal disease, is almost always characterized by a similar type of obesity. The major distinguishing feature between primary gonadal disease and Frohlich's syndrome is the uniformly high titer of urinary gonadotropins present in the former.

Obese boys and girls with delayed sexual maturation are most commonly confused with instances of Frohlich's syndrome. The distinction between the two groups must frequently await passage of a suitable period of time, since the former group will eventually develop normally. In addition, this group has no evidence of any intracranial disease.

Prognosis. — The prognosis is dependent on the nature of the underlying disease process. Where the syndrome results from an old quiescent inflammatory process, life is not threatened. In the presence of an intracranial tumor, the outlook is less certain and dependent essentially on the nature of the tumor present. Whether the disease is due to inflammatory or neoplastic changes, spontaneous recovery from the endocrine symptoms does not generally occur.

Treatment. — The treatment consists of two phases, one directed toward the underlying intracranial process, the other toward the endocrine abnormalities. When the syndrome is associated with pituitary or hypothalamic tumor, either *x*-ray or surgical treatment must be employed, depending upon the nature of the tumor and the presence or absence of progressive mechanical pressure symptoms.

The therapy of the endocrine manifestations consists of the control of the obesity, if possible, through the use of suitable dietary restrictive measures, plus the daily oral administration of thyroid extract. Treatment of the hypogonadism should first be attempted with chorionic gonadotropin, with the hope that the gonads may be stimulated to increased size and improved function. For this purpose 500 to 1500 units of chorionic gonadotropin is administered intramuscularly 3 times a week for a period of six weeks, followed by a two month rest period, and then a repetition of the course of therapy for another six weeks. If no improvement occurs in the hypogonadism upon completion of two such intensive courses, the likelihood of obtaining any further improvement with this form of therapy is negligible. In such an event, substitutive therapy with testosterone or estrogen, depending upon the sex of the patient, should be instituted. This substitutive treatment ought not to be started until one is reasonably certain that spontaneous sexual maturation will not occur.

Illustrative Case

The following case has been reported by Beckmann and Kubie.[3]

A fourteen year old boy complained of recurrent headache, amblyopia, and giddiness of several months' duration. On one occasion he had lost consciousness.

Physical examination revealed an infantile obese boy with large, rounded breasts and fat pads over the abdomen, thighs and buttocks. There was no axillary or pubic hair. The external genitalia were minute in size. Visual acuity was markedly reduced. In the right eye there was a loss of the inferior quadrants, and in the left eye there was a loss of all but the superior temporal quadrant.

X ray revealed a small sella turcica with the anterior clinoids apparently turned in The glucose tolerance test was normal

An inoperable tumor was found at operation, and the patient died shortly thereafter

At autopsy, a large suprapituitary cyst was found extending backwards under the crura and adjacent to the pons The pituitary body was normal in size but had been pushed down by the tumor Histologically the tumor was an adamantinoma The thyroid was small and the testes were markedly hypoplastic

LAURENCE-MOON-BIEDL SYNDROME

The Laurence Moon Biedl syndrome is characterized by the presence of obesity hypogenitalism retinitis pigmentosa, polydactylism syndactylism and mental retardation

The recorded history of this syndrome dates back to 1866 when Laurence and Moon[79] reported 4 cases of retinitis pigmentosa occurring in members of the same family, associated with other abnormalities including hypogenitalism obesity mental deficiency, and dwarfism During the next fifty years there were many references in the literature to patients with retinitis pigmentosa and other evidences of this syndrome without an awareness on the part of the authors of the clinical entity as a whole In 1920, Bardet[80] reported an instance of the association of these various defects and recognized that they constituted a unit syndrome Two years later Biedl[81] reported 2 cases occurring in a family and emphasized that various other congenital malformations such as anal etresia and deformities of the skull could occur

Approximately 150 instances of this entity have been reported to date From a consideration of the cases in the literature together with their pedigrees it is apparent that the syndrome may occur in an incomplete form When full blown it includes obesity hypogenitalism associated with a paucity of facial axillary and pubic hair high pitched voice and soft textured skin dwarfism retinitis pigmentosa polydactylism mental defects and a familial history in which other members of the family have manifested the complete syndrome or parts of it In addition to the ones already mentioned there are a variety of congenital malformations which may be encountered These include various cranial defects such as oxycephaly and hydrocephalus facial palsies ptosis of the eyelids kyphosis lordosis deaf mutism infantile glaucoma and congenital heart disease These patients often manifest various neurological abnormalities such as nystagmus ataxia and a staggering weaving gait[82, 83, 84]

The syndrome is more common in males in an approximate ratio of 64 to 36[83] and in approximately a fifth of the cases there is a history of consanguinity in the parents The disease occurs in both Negroes and whites In only 53 per cent of the patients is there both adiposity and hypogenitalism[84] The remaining patients may either show one alone or neither of these manifestations[85, 86]

Etiology and Pathology —The cause of this disease is unknown Satisfactory autopsy records are available in 6 patients with the syndrome[87, 88, 89, 90, 91] The reported pathologic findings in the brain were by no means uniform in these 6 patients In 2 there was a marked increase in the

number of basophil cells in the adenohypophysis. In 1 of these 2 patients in whom actual pituitary cell counts were performed the basophil cells numbered 42 per cent in contrast to the 11 per cent which is normally observed. In a third case the sella turcica was enlarged and contained a cyst in the walls of which were epithelial rests. In this patient only a very small amount of pituitary tissue was evident in the stalk, the remainder having been destroyed by the cyst. In a fourth patient there was a normal hypophysis, but a small band-shaped hyalinized area devoid of nuclei was found in the pituitary stalk. This patient in addition had an exotosis of the inner table of the frontal bone. In the remaining 2 patients the hypophysis was apparently normal. The brains of these cases showed a diffuse reduction in ganglion cells with a predominantly astrocytic gliosis most marked in the marginal and subependymal regions. There was fibrosis of the blood vessels of the brain associated with a developmental defect in the muscular coat and the presence of myomatous nodules in the lumina of the larger vessels. In none of the 6 cases reported was there any significant alteration in the hypothalamus, although in 1 patient there seemed to be some reduction in the number of glial cells. In 2 male patients and 1 female there was a report of the pathologic findings of the other endocrine glands. In the 2 male patients aged nineteen and fifteen years the prostate, seminal vesicles and testes were hypoplastic. In the testes there was no evidence of maturation of spermatozoa although the germinal epithelium appeared quite normal. In one instance there was considerable hypoplasia of the interstitial cells and in the other the cells were only slightly reduced. In the female patient aged seven the uterus, ovaries and tubes were abnormally small and the ovaries contained a few primordial follicles. In all 3 patients the adrenals, pancreas and thyroid were reported to be normal. In addition Roth[14] described testicular biopsy studies in 5 male patients with the Laurence-Moon-Biedl syndrome. Four of these patients were brothers who demonstrated the complete syndrome while the fifth presented retinitis pigmentosa, polydactylism, mental retardation, slight obesity but no hypogonadism. In the 4 brothers who presented the complete picture the penis and testes were infantile in size and microscopic study of the testes showed the tubules to be small and populated principally by Sertoli cells. In 3 of these 4 patients there was some spermatogonia and in the fourth none at all. In all 4 patients there was moderate sclerosis and hyalinization involving most of the tubules and complete sclerosis and hyalinization in a few. The fibroblasts were increased and no interstitial cells could be identified. In the fifth patient, the one with the incomplete syndrome, there was normal spermatogenesis and normal interstitial cells.

The marked familial incidence of the disease had stimulated a good deal of interest in the genetic aspects of the problem. Of the two main theories one is that one gene produces all the signs and that incompleteness of the syndrome is due to the action of modifying genes; the other is that the syndrome is determined by two or more genes. The former view is favored by Sorsby and his colleagues.[63] In any event one gene appears to affect the development of the ectopic zone of the prosencephalon (ectoderm) and thereby the hypothalamus, infundibulum, optic chiasm and retina, resulting in obesity, genital dystrophy, retinitis pigmentosa and mental defi-

ciency The other gene affects the mesoderm for the skeletal abnormalities

Laboratory Findings —In the 4 patients with the complete syndrome described by Roth [9] there was a reduction in the urinary excretion of the 17 ketosteroids and a low gonadotropin titer in the urine The urinary neutral 17 ketosteroids varied from 3 2 to 6 3 mgm /24 hours while there was less than 4 mouse units of urinary gonadotropin In the fifth patient the one with the incomplete syndrome without hypogonadism both the urinary neutral 17 ketosteroids and pituitary gonadotropin titer were normal

Treatment —*In young patients treatment with chorionic gonadotropin* should first be instituted in an attempt to promote development of the gonads Hence as in the patients with Frohlich s syndrome 500 to 1500 units of chorionic gonadotropin is administered intramuscularly 3 times a week for a period of six weeks with a repetition of the course after a two month rest period If there occurs no response to this form of therapy which is most likely then substitutive therapy with androgens or estrogens depending upon the patient's sex should be instituted

Illustrative Case

The *following case was previously reported from the Mount Sinai Hospital* by Marmor and Lambert [93]

A twelve year old Cuban boy was referred to the Consultation Service of the Mount Sinai Hospital There was no parental consanguinity One relative *on the father s side was said to have had polydactylism The patient an only* child was born with 6 toes on each foot and the extra toes were removed shortly after birth His development was apparently normal up to the age of six years when his mother noted that his vision was poor At about this time *he also began to gain weight rapidly*

Physical examination revealed the boy to be 4 feet 11¾ inches (151 8 cm) tall and 136¹ pound (62 Kgm) in weight He was short and obese with a typical feminine type of fat distribution about the breasts and hip and a *suprapubic fat pad The face was rather large Prominent raphes were evident* on the hard palate The fingers were tapering There was a scar of the excised sixth toe on each foot The penis was small No pubic hair was present The median raphe and the corrugation of the scrotum were lacking The testes had *descended The skin was soft and the hair silky*

Examination of the eye revealed the visual field to be markedly contricted but central vision was well preserved There was a sparse but definite deposit of pigment in the periphery of each fundus which was superficially placed *and of a bone corpuscle type*

The patient showed no gross behavior disturbance and exhibited a rather placid disposition His mental age according to the Terman revision of the Binet Simon test was nine years giving him an intelligent quotient of 70 *placing him in the high grade moron group*

Laboratory findings were essentially negative The basal metabolic rate was —16 per cent The glucose tolerance test was normal A roentgenogram of the skull showed that the sella turcica was normal in size and shape No *erosion of the clinoid process* no evidence of increased intracranial pressure and no unusual shadows in the cranial vault were observed

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Section II The Adrenals

Chapter 6

THE ANATOMY, MORPHOLOGIC STRUCTURE AND EMBRYOLOGY OF THE ADRENALS

Gross Anatomy of the Adrenals — The two suprarenal glands in man sit astride on the upper poles of the kidneys. The convex surface of the kidneys produces a concave impression on the glands. The right suprarenal body is somewhat triangular in outline and its anterior surface touches the inferior vena cava posteriorly and medially and the liver laterally. The left adrenal is less triangular and more crescentic in outline, lies along the anterior medial border of the left kidney and its lower half is in contact anteriorly with the posterior surface of the pancreas and splenic vessels. Frequently the left gland is elongated and may extend down to the hilus of the kidney, actually touching the renal vessels. It is somewhat nearer the aorta than is the right one and lies behind the lesser omental sac. Both glands are situated in the epigastric region at about the level of the 11th thoracic vertebra. The posterior surfaces rest against the lumbar insertion of the diaphragmatic leaves.

The glands are enclosed in a tough connective tissue capsule and embedded in adipose tissue. This connective tissue capsule penetrates into the deeper parts of the gland. It is contiguous with the septa which divides the organ into its characteristic zonal layers. In addition the glands are surrounded by renal fascia to which they are quite firmly attached. The upper part of the lateral surface of the right gland is devoid of a peritoneal covering while the lower half is covered by peritoneum. On the other hand the upper anterior surface of the right adrenal is covered by the peritoneum of the omental bursa while the lower area is free of such peritoneal covering.

On the anterior surface of both adrenals a faint groove is discernible where the central vein appears on the surface. The adrenals have an unusually rich blood supply. The superior, middle and inferior suprarenal arteries which are branches of the inferior diaphragmatic artery, aorta and renal artery respectively penetrate into the interior of the gland to supply the cortex and medulla separately. The medulla in contrast to the cortex has a well developed venous supply and eventually all the venous channels empty into one large central vein in the medulla which exists at the hilus as the suprarenal vein. On the right side this vein drains into the inferior vena cava while on the left side it empties into the renal vein.

The lymphatic channels of the adrenals form two plexuses, one directly under the capsule and another one in the medulla. The peripheral plexus

nest is the *zona glomerulosa* In this area the cells are grouped rather loosely together in ill-defined clusters The layer closest to and surrounding the medulla is the *zona reticularis* The cells in this region are arranged in an irregular network possess fine lipoid droplets and considerable pigment These pigment granules are probably degenerative or aging manifestations and are probably identical with the lipofuscin found in other organs of the body Aschoff has referred to this adrenal cortical pigment as the "wear and tear" pigment The *zona fasciculata* represents the layer of cells between the *zona glomerulosa* and the *zona reticularis* This zone is by far



Fig 10 —Section of adrenal of a child *ka* capsule *bg* blood vessel *n* nerve trunk Cortex *zgl* zona glomerulosa *zfl* zona fasciculata *zre* zona reticularis *ma* medulla *msi* medullary blood sinuses *nz* nerve cells (After Krause 1921)

the widest of the layers Its cells are arranged in strands which extend parallel to one another from the glomerular to the reticular layers The cells of this zone are particularly rich in fat There is considerable evidence to indicate that new cortical cells are constantly being formed in the inner part of the glomerular and outer part of the fascicular layer and as they age they migrate towards the reticular zone from which they are finally removed Ingle[10] recently demonstrated the regeneration of adrenal cortical cells from the enucleated capsule following the continuous parenteral administration of adrenocorticotropic hormone in the rat Greep and

communicates with the efferent lymphatics in the perirenal capsule while the central one follows the central and suprarenal veins The lymphatics of *the right adrenal drain into lymph nodes near the aorta* and near the crus of the diaphragm On the left side they connect with a lymph node situated at the origin of the renal artery and with nodes between the aorta and the crus of the diaphragm Occasionally the left sided lymphatic channels will follow the splanchnic nerve through the diaphragm and empty into mediastinal nodes

The adrenals are innervated chiefly by branches of the splanchnic nerves These nerves then form the suprarenal plexus and connect with the renal and celiac plexuses and the celiac ganglia

The combined weight of both adrenals in the human varies considerably dependent on a number of factors discussed elsewhere in this book The *average weight of each gland is approximately 3 to 5 grams* They vary from 40 to 60 millimeters in length 20 to 30 millimeters in width and 2 to 8 millimeters in thickness except at the bases where they are considerably thicker The cut gland consists of an outer cortical layer and an inner medullary layer The latter constitutes about 10 per cent of the weight of the gland The cortex or outer portion is firm and distinctly yellowish in color due to the presence of lipid filled cells while the medulla is somewhat softer more pulpy and of a dark reddish brown hue The trabeculae from the capsule penetrate into the gland and form septa which divide the cortex into its three characteristic zones the *zona glomerulosa zona fasciculata* and *zona reticularis*

Accessory Adrenal Tissue —Such accessory bodies may be made up of cortical tissue or chromaphil tissue alone or a combination of both structures resembling true adrenal glands in miniature These complete accessory bodies are more common in some animals than in others and are extremely rare in humans They are relatively uncommon in the cat or the dog but are observed fairly frequently in the mouse the rat and the rabbit *When present they usually are found in the connective tissue and fat* immediately surrounding the adrenals or in the cranial regions of the kidneys occasionally actually embedded in the kidney substance or protruding as a nodule from the adrenal itself

The medullary tissue of the adrenal glands is part of a widely distributed chromaphil system Hence accessory chromaphil tissue may be diffusely located almost anywhere in the body but does not constitute *in a true* literal sense accessory adrenal glands Accessory cortical bodies made up entirely of cortical tissue are found not infrequently and may be located in the adrenals themselves in the connective tissue and fat surrounding the adrenals and in almost any region of the abdominal cavity Such nodules have been found in the pelvis in the broad ligaments of the uterus along the course of the genitourinary tract in the scrotum and the vaginal wall, and even in the liver and pancreas

Histology of the Adrenals —A cross section of the adrenals reveals a deeply yellow outer portion the cortex and a central reddish hued area the medulla The medulla constitutes approximately one tenth of the total adrenal cross sectional width The cells of the cortex are arranged in three layers from without inward The outermost layer which is also the thin

versally true The general thickness and structure of the adrenal cortex differs with age in humans During fetal development the adrenals attain an enormous size and at birth the cortex really consists of two parts, a large fetal cortex or X zone, and a considerably smaller outer layer of cortical cells identical with that observed later in life The reduction in size of the adrenal cortex after birth is due essentially to the rapid degeneration of the X zone which disappears almost entirely during the first few months of postnatal life[1] leaving behind the true cortex which continues to grow and develop The growth of the latter becomes considerably accelerated just before and during puberty, and continues to grow, although at a much slower pace, probably until adult middle life It is interesting to note that in the human fetus, the adrenals consist almost entirely of cortical cells (X zone and true cortex) The reticular zone of the adult cortex corresponds in position to the X-zone It is probable that the postnatal reticular zone originates at an early age from persistent cells of the fetal reticular zone (X zone) which fail to undergo involution However the cells of the postnatal reticular zone are not identical with the cells of the X zone, although the cells of the former develop and differentiate from the latter [2] The true functioning adrenal medulla of man is a postnatal development, and its growth is associated with a simultaneous degeneration of the extra adrenal chromaphil tissue

In man the cells of the medulla are irregularly arranged although their appearance is rather typical There are two kinds of cells in the medulla the irregularly arranged sympathetic ganglion cells and a large number of granular cells packed with chromaffin granules which yield a characteristic staining reaction with chromic acid The cells lie in a fairly rich connective tissue network more highly and extensively developed than in the cortex The blood supply is abundant and sinusoids are located in the intercellular meshes which permit of intimate contact between the cells and the blood

The cells of the adrenal cortex are particularly rich in lipoid granules of varying sizes Their fat like material is essentially of two kinds The doubly refractive substance appears to consist of cholesterol esters perhaps associated with lecithin [3] while the isotropic fatty inclusions consist of neutral fats and fatty acids This fatty material is present in all the layers of the adrenal cortex but is most abundant in the *zona fasciculata* where it is present in both small and large droplets The cells of the *zona reticularis* contain fine droplets of fat in relatively small amount associated with considerable pigment This is of interest in view of the fact that Mulon[4] has suggested that the adrenal lipoids play an intermediary role in the elaboration of pigment from mitochondria The fatty substance is in addition probably responsible for the formation of siderophil structures These structures, which appear coarsely granular in man are most commonly present in the deeper layers of the cells of the *zona fasciculata* Goormaghtigh[5] has suggested that the siderophil bodies result from a combination of cell proteins notably albuminoids with cholesterol or its esters

Recent cytologic and cytochemical studies have contributed important information to our knowledge of the adrenal [8,9] The *mitochondria* in contrast to the lipoid material is present not only in the cells of all the

Deane[16] have confirmed these observations and demonstrated that the regenerated cortex actually includes all three zones. However, other evidence would tend to throw some doubt upon this view. It has been observed that cell division occurs throughout the cortex. Similarly studies

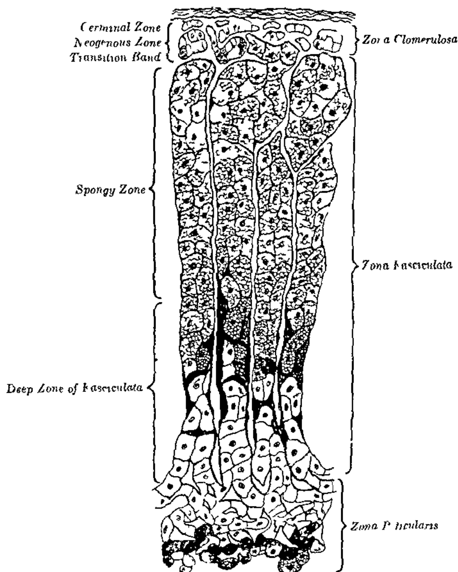


FIG 11 —Schematic representation of adrenal cortex (after Goormaghtigh)

with intravital dyes have failed to demonstrate any cell translocation. Finally, the failure of various cortical cell types to undergo cytomorphosis in tissue culture strongly suggests that the cortical cells arise, function and die in one zone.[8]

This general arrangement of cortical cells holds true for most mammals although a well defined division into its several layers is by no means uni-

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

zones of the adrenal cortex but in the medulla as well[6] In the cortex they are most readily observed in the cells of the glomerular zone while in the fascicular zone they are often concealed in the fat globules and can only be identified with the removal or absence of the fatty substance Mitochondria are even more abundant in the medullary cells where they may be more readily demonstrated than in the cortex They usually appear as small round, granular bodies and less frequently as rod like and filamentous forms These bodies have been found to be a useful index of cell function although no direct correlation with secretory activity can be established Similarly the Golgi apparatus may function as an index of the secretory activity of the cortical cells, being larger during cell activity and smaller during the resting phase

Ketosteroids have been identified in the lipid droplets of the adrenal cortex with the aid of various histochemical reactions characteristic of certain portions of the steroid molecule The phenylhydrazine, Schiff and semicarbazide reactions depend on the presence of a ketone or carbonyl group while Reichstein s ammoniacal silver reaction depends on the presence of a carbonyl group active enough to reduce ammoniacal silver The other tests include the Liebermann Burchardt reaction, the phenomena of birefringence and autofluorescence and solubility in acetone Although no single one of these reactions is specific for ketosteroids no other groups of compounds will give positive responses to this battery of tests

Employing these various criteria Greep and Deane[8] have demonstrated that hypophysectomy in the rat results in marked atrophy of the zona fasciculata and the zona reticularis while the glomerulosa remains relatively intact and indeed actually broadens This is associated with histochemical evidence of the disappearance of ketosteroids from the fascicular layer while the lipid content of the glomerulosa remains unaffected Somewhat earlier Reese and Moon[11] had noted that following the injection of adrenocorticotropic hormone there occurred a striking hypertrophy of the Golgi apparatus particularly in the outer portion of the fascicular layer The retention of the integrity of the zona glomerulosa following hypophysectomy is significant in that there is a considerable body of evidence which at least suggests the continued secretion of adrenal cortical salt and water retaining fractions following hypophysectomy[12 13] On the other hand the relationship of the fascicular layer to the elaboration of the 11-oxygenated corticosteroids is further emphasized by Greep and Deane[8] who demonstrated that injections of corticosterone into the intact rat result in alterations in the distribution of the sudanophilic material identical with those observed after hypophysectomy while the lipids of the glomerulosa remain essentially unaffected The adrenal response of normal rats to the injection of desoxycorticosterone is in sharp contrast to that which is observed to occur after the injection of the 11-oxygenated steroids Following injection of desoxycorticosterone there is a disappearance of lipid from the glomerulosa[14 15] Greep and Deane[8] approached this problem in a somewhat different fashion In the rat twenty-eight days after hypophysectomy when the lipids of the fascicular layer were greatly depleted and the zona glomerulosa was uninfluenced the administration of desoxycorticosterone for an additional period of a month resulted in a disappearance of the lipid

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and is completed at birth The medullary cells are ectodermal in origin since they are derived from the sympathetic ganglia The cells of these ganglia become differentiated into two types the sympathoblasts which eventually give rise to the mature sympathetic ganglion cells and the pheochromoblasts which subsequently develop into the characteristic chromaffin cells of the adrenal medulla The sympathochromaffin cells separate from the ganglia and in the 20 millimeter human embryo these cells migrate to the region of the cortical anlagen and penetrate the latter in cord like masses These cells finally unite in the interior of the cortex to form a single compact mass Actually it is not until the embryo has attained a length of 10 centimeters that the chromaphil cells have reached the central vein and formed a true medulla Along with the chromaphil cells sympathoblasts are also carried into the cortex and give rise to the sympathetic ganglion cells within the medullary tissue The penetration of the cortical cells by the sympathetic cells is accompanied by a folding and invagination of the cortical layers which permits of a more intimate contact between cortex and medulla

During the third and fourth months of fetal life the adrenals are enormous in size actually being somewhat larger than the kidneys From this point on they grow less rapidly in proportion to the contiguous organs and at the end of the sixth month are only one half as large as the kidneys At birth the adrenals are one third as large as the kidneys and with the degeneration of the X-zone they become progressively smaller so that the ratio of the adult adrenal to kidney is 1 28

In those species in which the two component parts of the gland remain separated the cortical tissue is referred to as the *interrenal organs* while the medulla is known as the *suprarenal organs*

are taken over by the extramedullary chromaphil tissue. The latter at best secretes only minute amounts of epinephrine and the adrenalectomized rat in which there is no extramedullary chromaphil tissue continues to live and grow when treated with potent cortical extracts. Certainly the laboratory effects of epinephrine on vascular tonus, carbohydrate metabolism and its emergency function as elaborated by Cannon[10] are well documented and well-observed phenomena. But the vascular tone of the adrenalectomized animal is promptly restored when treated with potent cortical hormones, while disturbances in carbohydrate metabolism and the loss of "emergency response" are corrected by certain fractions of adrenal cortical extract. Nevertheless, it is inconceivable that a substance as pharmacologically active as epinephrine does not play a very significant role in the body economy. Grollman[11] has suggested that its major function is to protect or act synergistically with the more vital and destructible cortical hormone. The evidence adduced for this hypothesis is, however, meager and at best decidedly equivocal.

In a general way, we may emphasize briefly the functions of adrenalin in relation to its effects on smooth muscle function, respiration and metabolism. It acts essentially on organ structures which are innervated by nerves of the sympathetic system and its effects are similar to those elicited when these nerves are stimulated. Outpouring of adrenalin will occur in response to a variety of physiologic, pathologic and pharmacologic stimuli. Thus, excitation of the hypothalamus, of the sympathetic fibers to the endocrine gland, emotional impacts such as fear and rage, increased muscular activity, sudden exposure to excessive heat or cold, asphyxia, hypoglycemia and severe hemorrhage will all induce release of epinephrine from the adrenal medulla. Certain pharmacologic agents such as acetylcholine and histamine will produce a like response.

Effect of Adrenalin on the Circulation.—Adrenalin exerts its effect on the circulation essentially through its action on the vascular tree and to a lesser extent because of its effect on the heart. It increases the contractility and irritability of the latter organ, frequently with the production of premature ventricular fibrillation. Adrenalin in adequate dosage can excite the idioventricular pacemaker in complete heart block, a phenomenon that is achieved through increased irritability of the heart muscle, and it will shorten the auriculo-ventricular conduction time when it is prolonged as a result of vagal stimulation. It increases the heart rate and cardiac output.

Its effect on the vascular tree is of a selectively paradoxical character. Adrenalin exerts its chief action upon the arterioles, although it also acts to varying extent upon the larger arteries, capillaries and veins. Its most widespread effect is to produce arteriolar constriction. This action on the arterioles is by no means universal but is limited to the vessels of the skin, mucous membrane and cerebrum, while it dilates the coronary vessels and the arterioles of striated muscle during the contraction phase of the latter. Finally, it apparently exercises no effect or very little effect on the pulmonary arterioles. The paradoxical action of this hormone serves a practical and protective purpose in that it permits increased blood flow in those structures where it is essential to the immediate maximum function

Chapter 7

PHYSIOLOGY OF THE ADRENALS

FUNCTIONS OF THE ADRENAL MEDULLA RELATION OF THE ADRENAL CORTEX TO ELECTROLYTE METABOLISM—TO RENAL FUNCTION—TO CARBOHYDRATE METABOLISM HORMONES OF THE ADRENAL CORTEX RELATION OF THE ADRENAL CORTEX TO THE URINARY EXCRETION OF THE NEUTRAL 17 KETOSTEROIDS AND THE 11 OXYGENATED STEROIDS

PHYSIOLOGY OF THE ADRENAL MEDULLA

THE first significant report was that of Vulpian[5] who noted a green coloration which occurred when the adrenal medulla was moistened with a dilute solution of ferric chloride It was promptly realized that some substance the exact significance and nature of which were not known at the time but which had a catechol nucleus was being secreted by the adrenal medulla In 1894 Oliver and Schaefer[6] demonstrated the remarkable blood pressure rise which followed the injection of an extract of the adrenal medulla Some eight years later Abel[7] succeeded in isolating a crystalline compound from the adrenal gland which he considered to be its active principle and which he called epinephrine

The origin of epinephrine in the body is obscure The close structural similarity which epinephrine bears to both tyrosine and phenylalanine would suggest that either of the latter two amino acids may be converted to epinephrine Actually such a transformation can occur in the test tube through the successive processes of oxidation methylation of the nitrogen atom and decarboxylation but *in vivo* experiments have failed to confirm the conversion of either tyrosine or phenylalanine into epinephrine However Nikolaeff[8] demonstrated that the perfusion of the isolated adrenal with a solution containing tyramine results in the formation of a substance having the properties of epinephrine This was subsequently confirmed by Schuller and Wiedemann[9] who found in addition that tyramine is formed in the kidney by decarboxylation of tyrosine

The physiology of the adrenal medulla is essentially a study of the pharmacology of epinephrine Since the isolation and identification of this hormone a voluminous literature has accumulated dealing with its properties and actions It would serve no purpose other than that of recapitulation to recount these studies in detail However certain aspects are worth re-emphasizing Despite our extensive knowledge of the actions of epinephrine its actual function in the body economy is obscure That the medulla the main source of epinephrine formation is not indispensable to life is evidenced by the fact that the totally adrenalectomized animal and the patient with Addison s disease will continue to live and thrive provided adequate cortical hormone therapy is administered One cannot assume that in the event of destruction or extirpation of the adrenal medulla its functions

sor of adrenalin and since it is not converted into adrenalin as rapidly as usual, due to adrenal disease, the dopa becomes fixed in the skin and is then converted to melanin through the action of the enzyme dopase

This ingenious hypothesis concerning the formation of melanin has some chemical basis in fact Barger[14] has shown that tyrosine is converted to dioxyphenylalanine which on further oxidation yields an indole carboxylic acid which can be transformed into dihydroxyindole This compound in turn may be condensed to a black pigment similar to the melanin of the skin Neuberg[15] demonstrated that epinephrine too, may be oxidized in the presence of certain oxidases to yield a black pigment similar to melanin In view of these reactions, it has been assumed that epinephrine tyrosine phenylalanine and dioxyphenylalanine are precursors of melanin

However this does not clarify the role that the adrenal plays in the excessive deposition of melanin in Addison s disease Since pigmentation occurs both in tuberculous disease of the adrenals where both the cortex and the medulla are destroyed and in Addison s disease due to atrophy of the cortex, where the medulla is relatively intact one finds it difficult to assume that the latter plays a vital part in pigmentation Similarly it is difficult to understand what role the cortex plays in this process, since the administration of whole cortical extracts or the various fractions thereof do not affect the pigmentation of Addison's disease to any remarkable extent To confuse the picture further classical instances of Addison s disease with the usual postmortem findings are reported in which no undue pigmentation was present during the entire prolonged course of the disease It is noteworthy too that in no bilaterally adrenalectomized animal has any undue deposition of the pigment in the skin been observed More recently, melanin pigmentation has been observed to occur in some patients following prolonged treatment with adrenocorticotropic hormone and with cortisone[2] One must conclude that at present the pathogenesis of the pigment melanin at least in Addison s disease is still obscure

Recent studies indicate however that the physiologic functions that are attributed to epinephrine may have to be reappraised Commercial epinephrine has been demonstrated to contain not only epinephrine but approximately 10 to 15 per cent of norepinephrine (arterenol nor adrenalin) This latter substance is the primary amine of epinephrine that is demethylated epinephrine It has also been found to be present in significant amounts in postganglionic adrenergic nerves of cattle[21] in the adrenal medulla of cattle[22] and in pheochromocytomas in humans[23] As with epinephrine the active and naturally occurring isomer is believed to be the levo form[25]

It is apparent at the present time that the theory of sympathin E and sympathin I formation as the basis of sympathetic function as advanced by Cannon and Rosenblueth in 1937[30] is no longer tenable It has been suggested however that epinephrine and nor-epinephrine represent sympathin I and sympathin E respectively although both drugs apparently have stimulatory as well as inhibitory effects It is possible of course that epinephrine or various related compounds in various proportions may be formed in various adrenergic nerve endings and that the manifestation

of the organism The contraction of the peripheral blood vessels results in an increase in the systolic arterial pressure, while the diastolic pressure falls somewhat

The most striking effect of adrenalin on the respiratory apparatus is that of relaxation of the smooth muscles of the bronchi It is this effect which makes it invaluable in the treatment of acute asthmatic episodes It has little or no effect on the pulmonary vessels, and very questionable effect on bronchial secretion

Adrenalin affects the total metabolism not only by increasing the basal metabolic rate, but also by influencing carbohydrate metabolism It increases the blood sugar by causing a disappearance of muscle glycogen and increasing the rate of glycogenolysis in the liver The breakdown of the muscle glycogen results in an increase in lactic acid the greater part of which is subsequently converted into and stored in the liver as glycogen

Its effect on the gastrointestinal tract is to decrease the motility and tone of the gastric and intestinal musculature The sphincters contract and there is some inhibition of secretion Similarly in its effect on the skin it inhibits sweating and calls forth a pilomotor response

The development of an operative procedure within recent years for the treatment of hypertension has again raised the question of the significance of the adrenal medulla and extra medullary chromaphil tissue The rate of secretion of epinephrine is readily affected by impulses from the splanchnic nerves and it is not unreasonable to assume that these nerves normally control the rate of such secretion Feldberg and his coworkers[12] have probably correctly concluded that the action of the splanchnic impulses is *mediated through acetylcholine which acts as a humoral transmitter* Sympathectomy and splanchnicectomy the operative procedure of choice certainly produces a fall in blood pressure but this is essentially transient since in the large majority of instances hypertensive levels are again subsequently attained *The further significance of these clinical experiments* lies in the fact that these patients manifest no undue physiologic abberations which can be attributed to adrenal medullary insufficiency However the antithesis of this was observed in patients with pheochromocytoma and paraganglioma With the development of our knowledge of the actions of epinephrine the clinical picture associated with such tumors becomes clear It was evident that the characteristic signs and symptoms the episodes of nervousness trembling sweating and pallor periods of paroxysmal severe hypertension and hyperglycemia and glycosuria were due to the secretion and liberation of excessive amounts of epinephrine

One further point about the metabolism of epinephrine may be worth considering and that is the role that it plays in pigmentation This is of course, particularly significant in Addison s disease where one of the classical features of this disease is the development of extensive pigmentation of the skin due to melanin Brown-Sequard suggested that a precursor of adrenalin is transformed into melanin Block[13] demonstrated that an isolated piece of skin if soaked in dioxyphenylalanine (Dopa solution) becomes darkly pigmented He then advanced the hypothesis that pigmentation is due to the presence of a specific oxydase in the skin, which forms melanin from dioxyphenylalanine This substance may be a normal precur-

nificant role in endocrine function than was originally suspected. Under stress and perhaps even under normal physiologic circumstances this hormone may function as a trigger mechanism influencing the activity of the anterior lobe of the pituitary, which in turn affects the function of other endocrine glands.

The demonstration and identification of epinephrine as an adrenal medullary hormone unquestionably represented a great step forward in our understanding of the physiology of the adrenals, but in a sense it served to retard further studies dealing with adrenal physiology for a considerable period of time. With the interest attached to the discovery of epinephrine the possibility of the existence of other adrenal hormones was lost sight of until the middle 1920's. It was only after extensive therapeutic trials and failure of epinephrine in Addison's disease that it was realized that this hormone by no means represented the vital hormone of the adrenals and further study of adrenal function was thus stimulated.

One may state unhesitatingly that the adrenal cortex is indispensable to life, that it secretes a number of hormones the exclusion of which from the body of man or of animals results in a rapidly fatal outcome. During the past two decades considerable advances have been made both in our understanding of the physiology of the adrenal cortex and in our knowledge of the elaboration of its hormones.

The physiology of the adrenal cortex is intimately concerned with

1) Electrolyte metabolism
2) Carbohydrate metabolism
3) Renal function
4) Growth of young animals
5) Resistance to stress
6) Relation to blood pressure and
7) Muscular response

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physiologically depends on the relative proportions of the various compounds present [8, 79]

The difference in cardiovascular response to epinephrine or nor-epinephrine may be used as an example emphasizing the differences in the physiologic effects of these compounds. The administration of epinephrine results in a marked increase in cardiac output due to a marked increase in heart rate, although there is a concomitant fall in peripheral resistance. The systolic blood pressure rises markedly, the mean arterial pressure moderately, while the diastolic pressure may remain unaltered. Following nor-epinephrine, the cardiac output is unchanged and associated with a slowing of the pulse rate. The peripheral resistance is markedly increased and as a consequence the systolic, diastolic, and mean arterial pressures rise considerably.[2,4] Finally, nor-epinephrine exercises no effect on the adenohypophysis while epinephrine stimulates the latter gland to the secretion at least of ACTH and thyrotropin.

The Effect of Epinephrine on the Function of the Anterior Lobe of the Hypophysis, the Adrenal Cortex, and the Thyroid.—Long and Fry[231] have demonstrated that epinephrine administered either subcutaneously or intravenously causes an unmistakable fall in adrenal cholesterol and ascorbic acid, and that this effect is abolished by hypophysectomy. Since a decrease in adrenal ascorbic acid and cholesterol reflects an increased formation of cortical hormone, this effect of epinephrine may be explained by the fact that the latter stimulates the secretion of adrenocorticotropic hormone from the adenohypophysis either directly or indirectly. Sayers and Sayers[1] have suggested that the administration of epinephrine or the onset of stress results in an increase in the peripheral utilization of adrenal cortical hormones, a consequent decrease in blood concentration of these fractions, and a resultant secondary outpouring of adrenocorticotropin. Long has suggested that two mechanisms probably exist. The one suggested by Sayers he believes is a slow controller of adrenocorticotropin production. More rapid secretion of this hormone, in his opinion, is brought about by means of a neurohumeral mechanism involving the liberation of epinephrine through a reflex arc and its direct action on the adenohypophysis. Epinephrine apparently does not act directly on the adrenal cortex, although it is possible that it may exert its effect through the hypothalamus as Hume[3] has suggested.

The role of epinephrine in the body defense mechanism is of considerable importance. Various traumata, such as exposure to cold, hemorrhage, injury to muscle and long bones, burns, etc., cause a prompt increased rate of formation of adrenal cortical fractions. The relation of these stresses to increased secretion of epinephrine is well known, and it is a reasonable assumption that the increased adrenal cortical secretion which occurs after trauma is due to the stimulating effect of epinephrine on the formation of adrenocorticotropic hormone.

In line with these observations, we and our coworkers have shown that the parenteral administration of epinephrine results in an increased secretion of thyrotropin from the adenohypophysis. This increased secretion of thyrotropin is inhibited by certain adrenal cortical fractions, particularly 11-dehydro-17-hydroxycorticosterone (Compound E)[33, 34] and by ACTH.

These diverse findings would suggest that epinephrine plays a more sig

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The demonstration and identification of epinephrine as an adrenal medullary hormone unquestionably represented a great step forward in our understanding of the physiology of the adrenals but in a sense it served to retard further studies dealing with adrenal physiology for a considerable period of time With the interest attached to the discovery of epinephrine the possibility of the existence of other adrenal hormones was lost sight of until the middle 1920's It was only after extensive therapeutic trials and failure of epinephrine in Addison's disease that it was realized that this hormone by no means represented the vital hormone of the adrenals and further study of adrenal function was thus stimulated

One may state unhesitatingly that the adrenal cortex is indispensable to life that it secretes a number of hormones the exclusion of which from the body of man or of animals results in a rapidly fatal outcome During the past two decades considerable advances have been made both in our understanding of the physiology of the adrenal cortex and in our knowledge of the elaboration of its hormones

The physiology of the adrenal cortex is intimately concerned with

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12

in the crisis of Addison's disease and in the bilaterally adrenalectomized animal may be essentially described as follows The initial change that occurs is a loss of sodium and chlorides in the urine The sodium ion is intimately concerned with water metabolism and is present in the intercellular fluid in isotonic concentration The excretion of sodium carries with it a certain amount of water each milliequivalent of sodium being excreted with approximately 6 5 cc of water The significance of this can be gauged if we bear in mind that in untreated adrenal cortical insufficiency there is a daily negative sodium balance of about 50 to 100 milliequivalents Translated in terms of water balance it would mean that such a patient loses daily 300 to 650 cc of water above his normal daily fluid loss

It is important to consider the site of origin of this fluid and the disturbance in the internal milieu which occurs as a result of it Gamble[26] has pointed out that the fluids in the body are present essentially in two compartments the extra cellular fluid which comprises about 20 per cent of the body weight, and the intracellular fluid, which represents about half the body weight The electrolytic content of these two compartments is quite different, although the osmotic pressure on both sides of the cell membranes remains fairly equal The extracellular fluid is a blood dialysate es entially protein free and its major ionic base is sodium The acid ions, chloride, bicarbonate organic acids and minute amounts of protein exercise practically no effect on the osmotic pressure and their ionic concentration is automatically regulated through respiration and renal excretion to equal that of the total base In the extracellular fluid therefore the sodium determines the osmotic pressure In the intracellular fluid on the other hand the major base is the potassium ion while the acid ions consist of phosphates bicarbonate, sulfates and protein The exchange of water between the cells and the interstitial spaces is determined and regulated by the osmotic pressure on each side of the cell membrane The volume of the blood plasma tends to remain constant under normal circumstances despite variations in fluid intake at the expense of the interstitial fluid, the latter acting as a reservoir which adds fluid to or removes it from the plasma as the needs dictate However when the volume of the extracellular fluid is materially decreased this will be reflected in a corresponding decrease in the plasma volume as the latter contributes its fluid stores to the interstitial spaces in an attempt to maintain the internal milieu intact In adrenal cortical insufficiency the salt and water lost in the urine comes primarily from the extracellular fluid This depletion of the sodium ion results in a decrease in the osmotic pressure of the interstitial fluid relative to the cell In an effort to maintain equal osmotic relationships fluid migrates from the interstitial tissue into the cell thus further depleting the fluid stores from the former compartment. Because of the character of the cell membrane osmotic relationships cannot be adjusted by migration of ions out of the cells into the interstitial spaces The dehydration so characteristic of adrenal insufficiency occurs therefore on at least two bases—the loss of salt and water from the extracellular fluid in the urine, and the further loss of fluid from the tissue spaces into the cell With a progressive loss of intercellular fluid there then occurs a decrease

of blood volume These changes if uncorrected go on to the development of shock It is this picture of shock which we speak of as an addisonian crisis

The loss of sodium and chloride in the urine in adrenal insufficiency was readily susceptible of proof but the loss of fluid from the tissue spaces into the cells was more difficult to demonstrate Harrison and Darrow[27] approached this problem by analysing muscle tissue obtained from both adrenalectomized and normal animals and found that with a decrease in the sodium content of the extracellular fluid there occurred an increase in the fluid content of the cells This hypothesis is further borne out by some experimental observations made by Harrop and his coworkers[8] in bilaterally adrenalectomized dogs They observed that in these animals dehydration hemoconcentration and shock will occur even though a negative water balance is prevented by increasing the fluid intake Since excessive fluid in these experiments is not lost through diuresis and since dehydration and hemoconcentration nevertheless ensue some redistribution of body fluids must occur to account for these phenomena In another series of experiments Harrop and his coworkers[9] showed that following the administration of cortical extract to the adrenalectomized dog in insufficiency there occurred a secondary diuresis This was associated with an increased urinary excretion of potassium phosphates and urea This potassium diuresis probably represents an excretion of intracellular fluid due to both cell shrinkage and cell destruction as evidenced by the negative nitrogen balance during this period During the period of secondary diuresis the experimental animals clinical condition has considerably improved and there has occurred an increase in the plasma concentration of sodium and chloride ions *Another approach to this same problem was attempted by* Swingle and his associates[30] They observed that the typical signs and symptoms of crisis occurred in anuric bilaterally adrenalectomized animals from which cortical extract was withheld These animals obviously could not have lost any sodium in the urine but nonetheless dehydration and shock occurred

One further channel to account for fluid loss in adrenal insufficiency must be considered and that is loss through the intestinal tract through vomiting and diarrhea *Both in the patient with Addison s disease and in the bi* laterally adrenalectomized animal vomiting and diarrhea do not occur until adrenal insufficiency has become well established Dehydration hemoconcentration and shock are already well developed when the dis turbing gastrointestinal symptoms manifest themselves These symptoms with their associated loss of sodium and chloride ions unquestionably con tribute to the final collapse but do not account for the progressive and severe fluid loss seen early in adrenal insufficiency The adrenal cortex however does play *a part in the degree of absorption* of sodium and chlo ride ions from the intestinal tract Thus in the adrenalectomized dog withdrawal of adrenal cortical extract produces a marked decrease in the rate of absorption of sodium chloride and potassium ions from loops of the ileum When extract is again administered this trend is reversed[31] In early insufficiency then there is not only present an excessive loss of

sodium and chloride but a decrease in absorption of these ions and hence fluids from the intestinal tract.

The adrenal cortex may play an important role in the primary regulation of water balance *apart from its effect on electrolytes*. The adrenalectomized animal and the patient with Addison's disease are unable to initiate the normal diuresis usually observed following excessive water ingestion. Water intoxication is easily induced under such conditions. An increased amount of antidiuretic principle has been found in the urine of the adrenalectomized animal. The osmotic pressure of the lost electrolytes overcomes the antidiuretic effect in part, but under conditions of forced hydration the effects of the antidiuretic factor are best noted. On the other hand, the administration of cortical hormones will produce a diabetes insipidus like state that is not very responsive to antidiuretic factor. Cortical hormones will restore in part the diabetes insipidus syndrome in a hypophysectomized animal.[236, 37]

Relationship of the Adrenal Cortex to Potassium Metabolism.—It is established that the *adrenal cortex plays a primary and vital role in the* metabolism of sodium. Whether it plays an equally significant role in the metabolism of potassium, or whether the latter is disturbed in adrenal cortical disease only secondary to alterations in the metabolism of the other electrolytes and in renal function is not quite so clear.

Potassium is essentially an intracellular ion and the total content of the human body has been estimated variously as averaging about 0.25 per cent. The body of a 70 kilogram man then contains about 175 grams of potassium. Of this total the extracellular spaces contain 3 grams, the blood plasma 0.3 gram, the blood 8 grams, and the remaining 164 grams are distributed in the various cells of the body, mostly the liver and muscles.[3] The body cells in general are fairly permeable to potassium, as indicated by the injection of radioactive isotopes of this ion.[33] However, under normal circumstances potassium remains within the cell principally because the cell membrane is impermeable to sodium and to all anions other than the monovalent ones[34] with which the potassium is combined. Generally speaking, potassium moves from the cell into the plasma in those conditions involving excessive loss of sodium and water from the body, such as occurs in severe hemorrhage, shock, adrenalectomy, intestinal obstruction, etc.[1] The function of potassium in the body economy is by no means clear. That it plays some *role in muscular activity is indicated by the fact that such* activity results in a loss of potassium in the cell in exchange for sodium. This loss of potassium is in some way related to the contractile process of muscle or their immediate recovery phase rather than acting as an agent in neuromuscular transmission of excitation. However, although it does not act as a humoral agent for neuromuscular transmission, it nevertheless plays an important part in the neuromuscular synapse. This is emphasized by the fact that potassium injections will re-establish contractions from nerve stimulation in a muscle that has previously been paralyzed by curare.[35] This effect on the neuromuscular function explains its beneficient influence in the treatment and prevention of episodes of familial periodic paralysis.[36] There is some evidence too of a relationship between carbohydrate and potassium metabolism. It apparently follows the carbo

hydrate cycle from muscle to liver and the reverse It frequently rises and falls with the lactic acid level as in exercise and shock It is affected by insulin and adrenalin in essentially the same way that glucose is[3] Potassium may be concerned with the production of phosphoric acid esters[37] although the question as to whether it activates the process of phosphorylation or the breakdown of hexosephosphate[38] is unsettled

In adrenal cortical insufficiency there occurs an elevation of the serum potassium This increase in concentration is associated with a decrease in the urinary excretion of potassium while the direct antithesis of this holds for the sodium ion With recovery from adrenal insufficiency there is an increase in the urinary excretion of potassium a decrease in that of sodium a concomitant fall in the serum potassium concentration and a rise in serum sodium The increase in the serum concentration of potassium observed during adrenal cortical insufficiency is associated with an increase in the potassium content of the intercellular fluid and of the cells[7] probably due to the failure of the kidneys to excrete adequate amounts of this ion

The behavior of the potassium ion in acute adrenal insufficiency as just described does not of itself point to any primary and fundamental relationship to adrenal cortical function The alteration in concentration of serum potassium may be secondary to the excursion of the sodium ion and water during insufficiency and after recovery A similar situation prevails in acute hemorrhage and in shock where adrenal cortical disease cannot be postulated The evidence advanced in favor of a direct relationship between the adrenal cortex and the metabolism of potassium is based on the following observations Ingle and his coworkers[39] have found that after bilateral nephrectomy in adrenalectomized rats the administration of adrenal cortical extract can still cause an appreciable fall in the concentration of potassium in the serum Further evidence was obtained from direct analysis of the tissues of adrenalectomized animals for potassium in which it was observed that there was an increase in the potassium concentration of the intracellular muscle fluid Administration of cortical extract reduced the elevated level of muscle potassium to normal values[27] Finally the administration of desoxycorticosterone to normal dogs eventually induced a drop in the serum potassium to almost half the control level and symptoms resembling those of familial periodic paralysis developed These symptoms could be relieved by the withdrawal of the hormone or the administration of potassium chloride[40]

The Relationship of the Adrenal Cortex to Renal Function —Acute adrenal insufficiency is associated with marked disturbance in renal function These disturbances are related to the dehydration reduction in blood volume and blood pressure and are characterized by an elevation in the non protein nitrogen This general picture of renal failure however, is indistinguishable from that observed in severe hemorrhage dehydration, or shock from any cause and is referred to as extra renal azotemia The extra renal azotemia whether due to adrenal failure or other causes of dehydration and shock is reversible by suitable therapy and hence is essentially of a temporary character

There is however another aspect of this problem of equally pertinent significance and that is the relationship of the adrenal cortex *per se* to

renal function This consideration is of fundamental importance since it raises the question of the site of action of the adrenal cortical hormones Shall we consider that the site of action of these substances is primarily on the kidney cells and that the entire train of events observed in the development of acute adrenal insufficiency is due to absence of such specific hormonal effects on the kidney cells? Or can we interpret the evidence of renal failure as part of the general picture associated with adrenal cortical insufficiency and lacking a primary and specific relationship to adrenal cortical function? This problem is difficult to answer The first and most obvious approach is an anatomic one Necropsy findings in patients with Addison s disease and in bilaterally adrenalectomized animals fail to reveal any consistent pathologic alterations in renal structure Guttman[41] in an analysis of 566 autopsied cases collected from the literature found that less than 10 per cent showed alterations in renal morphology sufficient to justify an anatomic diagnosis of kidney disease Barker[4] reported the autopsy findings in 28 cases of Addison s disease, and found that 10 showed *definite anatomic changes in the kidney* The changes observed were mostly those of tubular atrophy with a flattening of the epithelium and diminution in the amount of cytoplasm Talbott and his coworkers[43] studied the kidneys of 6 patients with Addison s disease who came to autopsy and found no renal anatomic abnormalities These results are similar to those in experimentally adrenalectomized animals in which no significant histologic changes were evident in the kidneys[44]

We can conclude from these pathologic studies that the kidneys of patients with Addison s disease or those of adrenalectomized animals show no consistent or significant alteration in renal structure However, the absence of gross or microscopic structural change does not exclude possible impairment of renal function specifically related to the lack of adrenal cortical activity This phase of the problem could only be investigated with advantage during intercritical periods when the patients with Addison s disease and the adrenalectomized animals were relatively well

The investigation of renal function with the usual clinical procedures, such as the determination of maximum urinary specific gravity the presence of albuminuria and the appearance of red blood cells and casts in the urinary sediment as well as the non protein nitrogen concentration in the blood and the phenosulfonphthalein excretion do not reveal any constant deviation from the normal in these instances It is essential to study specifically glomerular filtration and tubular absorption in order to determine the presence or absence of the more subtle alterations in renal function Talbott and his coworkers[43] conducted such studies in 10 patients with Addison s disease when they were relatively well had a normal blood electrolyte pattern and were maintained only on supplementary oral salt therapy The rate of formation of glomerular filtrate was determined by inulin clearance and was found to be definitely reduced in every instance investigated When these studies were repeated following the administration of desoxycorticosterone acetate or whole adrenal cortical extract there occurred a significant increase in the rate of formation of glomerular filtration although normal levels were never obtained The question promptly presents itself as to whether the depression of the rate of glomerular filtra

tion may not be due to a reduction in blood flow rather than to a specific alteration in glomerular function The results obtained with creatinine and diodrast clearance studies at low iodine plasma levels suggested that the depression of the rate of glomerular filtration is out of proportion to the reduction in renal blood flow Similarly, the observations of these authors on the maximum ability of the tubules to excrete diodrast and reabsorb glucose suggest that the tubular excretory function is well maintained while their ability to resorb at least as far as glucose is concerned is seriously impaired In more recent studies Waterhouse and Kentmann-[39] also noted a decrease in glomerular filtration and renal blood flow These investigators however suggested that the decrease in glomerular filtration was secondary to the decrease in renal blood flow

The relationship of renal function to water, sodium and potassium clearance is of more practical and immediate importance in a study of the adrenal cortex Talbott and his coworkers[43] found that there was no significant alteration in the tubular reabsorption of water either before or after adrenal cortical hormone therapy Similarly no dissipation of sodium was apparent while there occurred a definite increase in potassium excretion following treatment with potent cortical extracts This increase in urinary potassium excretion was produced mainly by an increase in glomerular filtration These results are in contrast to those obtained in adrenalectomized animals by Harrison and Darrow [44] These investigators found that the sodium clearance was increased while that of potassium was decreased when treatment with adrenal cortical extract was discontinued Resumption of hormonal therapy promptly restored these clearances to normal The observations of Harrison and Darrow[45] are probably correct in view of the electrolyte changes which occur in adrenal insufficiency and the known clinical and laboratory response of the blood electrolytes to specific hormone therapy

It is desirable at this point to summarize the relationship of the adrenal cortex to electrolyte and water metabolism and renal function The conclusions to be drawn are based on the studies of the pathologic physiology of the adrenal cortex Whether they apply to the physiology of the adrenal cortex under normal circumstances is at present impossible to know with any degree of certainty In any event disease or extirpation of the adrenals results primarily in an increase in the urinary excretion of sodium This is associated with a loss of water resulting in a depletion of the intercellular fluid At the same time fluid is further lost from the extracellular tissue spaces by its migration into the cells This depletion of extracellular fluid eventually results in a reduction in the circulating plasma volume When these factors become great enough dehydration and shock are produced Associated with an increase in the loss of sodium there occurs a loss of chloride although to a somewhat lesser extent, and a decrease in the urinary excretion of potassium with a consequent increase in the serum concentration of this ion The fact that more sodium than chloride is lost plays a part in the acidosis which is always seen in the adrenalectomized animals in insufficiency and frequently observed in man during crisis in Addison s disease The dehydration and shock induced by the salt and water loss with the consequent reduction in renal blood flow and pressure

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to minute amounts of insulin With the advent of a potent cortical extract the character of these carbohydrate disturbances could be more carefully evaluated Britton and Silvette[49] were the early proponents of the significance and fundamental character of changes in carbohydrate metabolism They demonstrated the occurrence of hypoglycemic seizures in adrenalectomized guinea pigs cats and other species phenomena not so readily observable in the adrenalectomized dog They further found that the liver and muscle glycogen of the adrenalectomized animals was considerably reduced and that the ability of these animals to form liver glycogen from injected dextrose or sodium lactate was diminished These observations received some clinical substantiation by Levy-Simpson[50] who demonstrated that patients with Addison s disease failed to show a rise in the blood sugar level comparable to that of normal individuals following the injection of a standard dose of epinephrine

The question arose too as to whether the carbohydrate disturbances observed were not due primarily to removal of the adrenal medulla This can be answered readily both from the clinical and experimental observations Patients with Addison s disease who have atrophy of the adrenal cortex but with relatively intact medullae nevertheless display the same characteristic disturbances in carbohydrate metabolism as do those patients with extensive and universal destruction of the adrenals due to tuberculosis Similarly Zwemer and his coworkers[51,52] found that in demedullated cats no changes in the blood sugar level occurred as a result of the operative procedure Boggild[53] observed similar results in dogs

It is evident from these few casual observations that alterations in carbohydrate metabolism occur both in patients with Addison s disease and in most adrenalectomized animals It is further evident that these disturbances are not related to destruction or removal of the medulla Let us examine the available experimental data which would indicate that the adrenal cortex plays a fundamental role in the changes in carbohydrate metabolism

Cori and Cori[54] showed that adrenalectomized rats which had been fasted for twenty four hours had practically no liver glycogen Long Katzin and Fry[46] working with adrenalectomized rats and mice found that so long as these animals are fed normal levels of liver and muscle glycogen can be maintained but when they are subjected to fasting a rapid depletion of liver glycogen ultimately followed by a similar reduction in muscle glycogen occurs The observation that fed adrenalectomized animals maintain normal stores of liver and muscle glycogen is contrary to the observations of Britton[55] This difference is probably due to the fact that the animals studied by Long and his group were maintained in normal electrolyte balance by the administration of sodium chloride It is entirely conceivable that in the presence of uncontrolled disturbances in the electrolyte pattern there may also be an impairment in the ability on the part of the tissues to store glycogen

Britton and Silvette[49] found that the low blood sugar and the depleted glycogen stores could be restored to normal by the administration of a potent cortical extract They similarly observed and this is of equal significance that the administration of cortical extract was capable of increasing

produces renal failure due essentially, therefore, to extrarenal failure. This entire process can be reversed promptly by the administration of adrenal cortical hormone. Under the influence of this therapy there occurs a decrease in the urinary excretion of sodium and chloride and an increase in excretion of potassium with a resultant elevation of the blood sodium and chloride levels and reduction in potassium concentration. With the retention of sodium, the intercellular fluid and the blood volume are replenished and the cellular fluid is decreased. Although the major alterations in the metabolism of potassium are secondary to those of sodium, there is some evidence to indicate that the adrenal cortex exercises some specific effect on potassium metabolism. Similarly the major renal functional alterations are secondary to the dehydration and shock which occur as a result of the sodium and water loss. But here, too, there is evidence to indicate that the adrenal cortex plays a specific role, although not of a very great magnitude, in the renal clearances of sodium and potassium.

The fact that patients with Addison's disease and the adrenalectomized animals are incapable of retaining sodium can be used as a test of adrenal cortical destruction.[1] Thus the administration of a salt free diet to patients with Addison's disease or to adrenalectomized animals will induce a negative sodium balance, a rapid depletion of intercellular sodium, a drop in blood sodium and hemoconcentration and within a short period of time will precipitate acute adrenal insufficiency. The individual or animal with intact adrenals when subjected to salt deprivation will respond with a marked reduction in urinary sodium excretion so that no depletion, either of fluid or sodium, of the intercellular spaces or blood occurs for a prolonged period of time.

Relation of the Adrenal Cortex to Carbohydrate Metabolism.—During the early period of investigation of the functions of the adrenal cortex attention was concentrated mainly on its effects on electrolyte metabolism. The relationship of the cortex to carbohydrate metabolism was a source of great conflict between those groups who insisted that the carbohydrate disturbances observed in the adrenalectomized animals were fundamentally related to destruction of the adrenal cortex and their opponents who postulated that these disturbances were nonspecific in character and rather related to the malnutrition so commonly present in the adrenalectomized animal. To some extent this difference in opinion concerning the significance of the disturbances in carbohydrate metabolism was due to differences in behavior of the adrenalectomized animals used. As Long, Katzin and Fry[46] have pointed out, in some species overwhelming changes in electrolyte metabolism occur so promptly as to obscure any alterations in carbohydrate metabolism. In others the animal survives long enough to permit these changes to become manifest.

It had been known for a long time that changes in carbohydrate metabolism do occur in the presence of destruction of the adrenal cortex. Porges[47] as early as 1910 pointed out the frequency with which hypoglycemic episodes occurred in patients with Addison's disease and that similar episodes occurred in adrenalectomized dogs. In 1925, which still represented the very early phase of the enlightened period in adrenal physiology, Maranon[48] demonstrated that patients with Addison's disease were markedly sensitive

renocorticotropin have thrown further light on this question Conn[illegible] has been able to induce temporary diabetes in man with this fraction However in a large group of patients studied by various investigators this type of alteration in carbohydrate metabolism was only infrequently encountered

Experience with the effect of the pure adrenal cortical steroids on carbohydrate metabolism is relatively limited In the rat however Ingle[illegible] has demonstrated the diabetogenic effect of 17 hydroxy 11-dehydrocorticosterone 17 hydroxycorticosterone and corticosterone as well as pituitary adrenocorticotropin He found that 11-desoxycorticosterone was diabetogenic in the depancreatized rats only when administered in massive doses 11-dehydrocorticosterone (Compound A) was not studied in the rat In the human however this compound in doses of 30 to 40 mgm a day failed to alter the glucose tolerance curve With doses of 60 mgm a day a distinctly higher glucose tolerance curve was obtained This compound does prevent the hypoglycemia of fasting in the patient with Addison s disease [illegible]

It is desirable at this point to summarize the various observations discussed Adrenalectomized animals that are well fed and maintained on sodium salts have a fairly normal blood sugar level and normal glycogen stores in the liver and muscles Starvation however causes a very rapid depletion of these stores and a drop in the blood sugar The administration of a potent cortical extract either to the fasting or fed adrenalectomized animal results in a replenishing of the liver glycogen and an elevation in the blood sugar level although it apparently exercises no effect on the muscle glycogen The ability of cortical extract to increase liver glycogen in the fasting adrenalectomized animal without affecting the muscle glycogen would suggest that the added glycogen must come from some other endogenous source The fact that there is an increased urinary excretion of nitrogen parallel to glycogen and glucose increase in the liver and blood following treatment with extract would suggest that the catabolism of protein strongly influenced by adrenal extract is the source of this endogenous glycogen This is further borne out by studies on phlorhizin diabetes in the fasting adrenalectomized animals The administration of cortical extract to these animals increases appreciably the urinary excretion of glucose A further point in favor of the significant role that the adrenal cortex plays in carbohydrate metabolism can be obtained from studies conducted with depancreatized and partially depancreatized animals Adrenalectomy in these animals modifies the severity of the diabetes while the administration of cortical extract enhances it Adrenal extract will cause an increase in the glycosuria in partially and totally depancreatized animals with intact adrenals Finally adrenalectomized animals are markedly sensitive to insulin,[illegible] and are incapable of converting precursor substances like lactic or pyruvic acid into glycogen or glucose

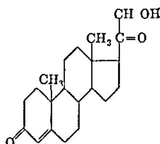
These observations would suggest that there is a very intimate relation between the adrenal cortex and carbohydrate metabolism Disturbances in this latter function in adrenalectomized animals and in patients with Addison s disease cannot be explained simply on the basis of a nonspecific phenomenon of the disease but rather must be assumed to represent as

the blood sugar level and glycogen reserves of normal animals. These observations were confirmed by Thaddea[56] and to a considerable extent by Long, Katzin and Fry.[46] The latter authors differed with Britton and Silvette in that they observed no effect of the cortical extract on the level of the muscle glycogen, although the hepatic stores and the blood sugar level were considerably increased. Long and his group[46] further found that the administration of cortical extract could prevent glycogen depletion of the liver in fasting adrenalectomized rats and mice. If the observations of Long and his colleagues are correct, that the store of muscle glycogen is not affected by cortical extract, it is curious that an elevation in the blood sugar level and an increase in the liver glycogen should occur in the fasting animal. It obviously cannot be explained by a shift in the glycogen store from muscle to liver, since the former is not affected. It must then follow that the additional glycogen is obtained from some other source. The bulk of the evidence would indicate that this glycogen is obtained by the catabolism of proteins. Evans[57] has shown that fasting adrenalectomized rats excrete about 25 per cent less nitrogen than do normal rats under similar conditions. This observation was confirmed by Long and his group.[46] In addition, they found that in both normal and adrenalectomized fasting rats and mice the administration of cortical extract was followed not only by an increase in liver glycogen and blood glucose, but that these were accompanied by a parallel increase in urinary nitrogen excretion. This would indicate that cortical extract intensifies the breakdown of protein with its conversion into glucose and accumulation of glycogen in the liver. Another approach to the same problem may be obtained by studying the effect of cortical extract on phlorhizin diabetes. Phlorhizin lowers the renal threshold for sugar, so that glucose is constantly being excreted in the urine as long as there are available exogenous and endogenous sources of sugar. Even in the fasting animals glucose continues to be excreted in the urine with the administration of phlorhizin. However, fasting adrenalectomized rats and dogs maintained in good health by the administration of sodium chloride excrete much less sugar after administration of phlorhizin than do normal animals similarly treated.[57] This defect is promptly corrected by treatment with whole adrenal cortical extract or certain crystalline fractions obtained from adrenal cortical extract.[58] These experiments would again suggest that adrenal cortical extract mobilizes the body protein, increases its catabolism and conversion to glucose.

Further evidence supporting the primary role that the adrenal cortex plays in carbohydrate metabolism is provided by *studies of the depancreatized* and partially depancreatized and adrenalectomized animal. Hartman and Brownell[59] and Long and Lukens have shown that adrenalectomy modifies in a favorable manner the severe diabetes produced by pancreatectomy in the cat. Long and his coworkers[46] further found that a similar effect could be obtained in the partially depancreatized rat. When adrenal cortical extract was administered to these animals the original severely diabetic state with marked glycosuria could be reproduced. These authors found in addition that cortical extract caused an increase in the urinary excretion of sugar in the partially depancreatized animal with intact adrenals. Sprague[61] confirmed these observations. Recent studies with ad

phous residue of great physiologic potency is left The number of steroid hormones isolated from adrenal cortical extract total at present 28 [75] Unquestionably, many more fractions will be extracted in the near future

Of all the steroid hormones thus isolated only those outlined in the preceding paragraph are known at present to have important physiologic significance and it is worthwhile to consider the nature of their activity



Desoxycorticosterone

Desoxycorticosterone causes a marked retention of sodium chloride and water and increases the urinary excretion of potassium and phosphorus [75, 76] At the same time it induces a marked fall in the concentration of sodium and chloride in the sweat However it exercises no effect on carbohydrate metabolism or the pigmentation of Addison s disease In Addison s disease and in experimental adrenal insufficiency it will restore the blood electrolyte pattern to normal increase the circulating blood volume and elevate the blood pressure The continued use of this hormone can result in edema and heart failure and in the temporary production of hypertension [77, 78, 79, 80] The hypertension thus induced bears no relationship to salt and water metabolism but is apparently a specific function of desoxycorticosterone It is interesting that while whole adrenal cortical extract will elevate the reduced blood pressure of the patient or animal in acute adrenal insufficiency to normal levels it will not induce hypertension Desoxycorticosterone however can cause the blood pressure to attain hypertensive levels but only in the presence of destroyed or extirpated adrenal cortices It is difficult although not impossible to induce hypertension in the normal individual or in the dog with intact adrenals with this hormone These facts would suggest that desoxycorticosterone has a specific hypertensive effect which is apparently normally balanced by other fractions of the adrenal cortex

It is of interest to observe that while this hormone has a pronounced salt retaining effect both in the presence of intact and destroyed adrenals it causes an increase in the urinary excretion of sodium in the presence of hyperfunction of the adrenal cortex [81] Thus in patients with Cushing s syndrome we have demonstrated that the administration of desoxycorticosterone followed by the intravenous injection of saline causes a considerable urinary outpouring of sodium in contrast to the behavior of normal individuals similarly treated in whom marked retention of the injected sodium is noted [81] There is no clear evidence to indicate the mechanism of this effect It is possible that either the injected desoxycorticosterone is

primary although perhaps not as important a defect is that of the electrolyte and water metabolism

THE HORMONES OF THE ADRENAL CORTEX

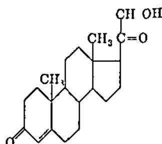
The attempt at substitutive therapy in the treatment of destructive diseases of the adrenals dates back to 1867[63] In 1903 Adams[64] collected a total of 97 cases of Addison s disease from the literature in which organotherapy was employed in the form of desiccated whole adrenal and the desiccated extract, and aqueous alcoholic and glycerine extracts used either by mouth or by injection Of this group of patients 16 were reported as permanently improved Among this group was a case reported by Osler[65] who responded particularly well to a glycerol extract of fresh sheep adrenal glands given both by mouth and by hypodermic injection When the use of the extract was discontinued the patient was precipitated into acute adrenal insufficiency which terminated fatally

These attempts at the manufacture of therapeutically efficacious cortical extracts were by far and large unsuccessful The extracts were crude and of a very dubious and at best limited potency and with the isolation of epinephrine further attempts at the isolation of cortical hormones were discontinued until the latter 1920 s In 1927 Rogoff and Stewart[66] succeeded in prolonging the survival period of adrenalectomized dogs with the use of saline extracts of whole adrenal glands They called this extract Interrenalin In the same year Hartman and his group[67] described an adrenal extract which prolonged the life of adrenalectomized cats This extract in contrast to that of Rogoff and Stewart contained no adrenalin In 1929 Pfiffner and Swingle[68] described the successful use of an alcoholic adrenal extract in adrenalectomized dogs The use of these various extracts in the treatment of patients with Addison s disease and the brilliant results obtained stimulated interest both in the attempt to fractionate the adrenal cortical extract and to manufacture synthetic cortical hormones Between 1936 and 1944 the important contributions to adrenal cortical organotherapy consisted in the isolation of various crystalline fractions of the whole extract

In 1936 and 1937 Mason Myers and Kendall[69] and de Fremery and his coworkers[70] isolated corticosterone and dehydrocorticosterone in crystalline form from the extracts of the adrenal cortex and found that they could maintain adrenalectomized animals in good condition A short while later Steiger and Reichstein[71] announced the synthetic preparation of desoxycorticosterone acetate from Stigmasterol Subsequently Reichstein and von Euw[72] succeeded in recovering this compound from an extract of the adrenal cortex In 1940 Pfiffner and North[73] isolated 17 β hydroxyprogesterone from the adrenal cortex In addition 17 hydroxy 11-dehydrocorticosterone or cortisone which is the compound E of Kendall and compound F of Pfiffner and Wintersteiner and 17 hydroxy-11-desoxycorticosterone or compound S[74] both hormones of important physiologic significance have been recovered from the adrenal cortex Other fractions of dubious significance and doubtful structure have been isolated After removal of the crystalline fractions from adrenal cortical extract an amor-

phous residue of great physiologic potency is left The number of steroid hormones isolated from adrenal cortical extract total at present 28[75] Unquestionably, many more fractions will be extracted in the near future

Of all the steroid hormones thus isolated only those outlined in the preceding paragraph are known at present to have important physiologic significance and it is worthwhile to consider the nature of their activity



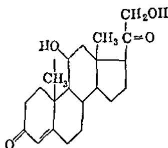
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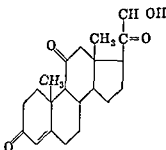
It is of interest to observe that while this hormone has a pronounced salt retaining effect both in the presence of intact and destroyed adrenals it causes an increase in the urinary excretion of sodium in the presence of hyperfunction of the adrenal cortex[81] Thus in patients with Cushing s syndrome we have demonstrated that the administration of desoxycorticosterone followed by the intravenous injection of saline causes a considerable urinary outpouring of sodium in contrast to the behavior of normal individuals similarly treated in whom marked retention of the injected sodium is noted[81] There is no clear evidence to indicate the mechanism of this effect It is possible that either the injected desoxycorticosterone is

converted, in the presence of hyperfunction of the adrenal cortex into a salt excreting hormone or stimulates the production of such a hormone The former hypothesis is by no means far fetched since the conversion of one hormone into the other would at least seem theoretically feasible in view of the close structural similarity between the various fractions

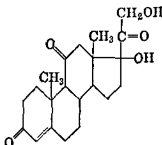
There is some evidence to indicate that the zona glomerulosa is concerned with the elaboration of the 11-desoxycorticosteroids Thus Greep and



Corticosterone



Dehydrocorticosterone



17 Hydroxy 11 Dehydrocorticosterone (Compound E of Kendall Cortisone)

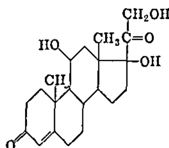
Deane[45] have demonstrated that the administration of desoxycorticosterone to the normal and the hypophysectomized rat results in a complete loss of lipids from this zone as well as a reduction in the sudanophilia and birefringence while the zona fasciculata remains unaltered They interpret these results as an indication of the cessation of the production of this hormone by the zona glomerulosa following the exogenous administration of extract This effect apparently does not require the presence of the

pituitary In addition Deane and Shaw [45] found that when rats are maintained on a completely salt free diet for a considerable period the glomerulosa first becomes broadened and contains an increased amount of lipid and subsequently becomes exhausted No significant changes occur in the layer when a sodium- and potassium free diet is used These experiments would suggest that when the sodium level in the blood is reduced in proportion to the potassium level the glomerulosa secretes an abnormally large amount of the salt conserving hormone and eventually becomes exhausted Deane and her coworkers conclude that the glomerulosa secretes the 11-desoxycorticosteroids and that it is capable of functioning independently of the pituitary

These three compounds in contrast to the action of desoxycorticosterone exercise a marked effect on carbohydrate metabolism and correct these defects in the adrenalectomized animal Following injections of these hormones glycogen is stored in the liver, the blood sugar levels are increased and hypoglycemia is prevented In addition 17 hydroxy 11-dehydrocorticosterone which has the most pronounced effect on carbohydrate metabolism is also capable of restoring the ability of adrenalectomized rats to form glucose from lactic and pyruvic acids However corticosterone and dehydrocorticosterone exercise only a minimal effect on blood electrolyte metabolism with a slight retention of blood sodium [87]

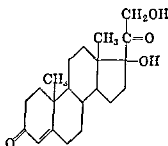
Recent studies in the human subject have extended our knowledge of the physiologic actions of compound I [59, 60, 61, 67, 7] The administration of this steroid in addition to abolishing the tendency to hypoglycemia of the fasting patient with Addison's disease decreases the sensitivity to insulin and may increase the level of the fasting blood sugar Urinary nitrogen excretion is increased Retention of salt and water may occur in the human subject With this retention of sodium chloride and water a marked increase in body weight attendant on edema may ensue The prolonged administration of this steroid will induce all the symptomatology of Cushing's syndrome as does also ACTH Rounding of the face acne hirsutism keratosis pilaris muscular weakness amenorrhea and depression or euphoria may occur The urinary corticoids will slowly increase in quantity reflecting a partial excretion of the administered steroids The urinary neutral 17 ketosteroids however are decreased suggesting the suppression of endogenous adrenal cortical function The hypochloremic hypokalemic alkalotic syndrome may be produced Negative balances of calcium and phosphorus may be induced because of the excessive loss of these ions in the urine and stool The urinary excretion of uric acid and creatine is usually increased but no change occurs in urinary creatinine Following the administration of cortisone there is a tendency towards an increase in serum albumen and a decrease in serum globulin in those instances in which the ratio is reversed To a lesser extent these trends are also discernible in normal sera The gamma globulin fraction may decrease There occurs a very slight increase in the total circulating leukocytes with a lymphocytopenia and eosinopenia No constant effect on the serum alkaline phosphatase nor total blood cholesterol is noted although the latter is sometimes increased and the former occasionally decreased Pigmentation has been reported in the patient with Addison's disease as well as in normal in

dividuals following the use of this steroid The antihyaluronidase activity of serum is increased



17 Hydroxycorticosterone (Compound F of Kendall)

This compound exercises a marked effect on carbohydrate metabolism similar to that of corticosterone dehydrocorticosterone and 17 hydroxy 11-dehydrocorticosterone



17 Hydroxy 11 Desoxycorticosterone

This compound exercises no effect on carbohydrate metabolism [84, 8] The effect of this hormone on mineral metabolism has not as yet been adequately investigated

When we examine the structural formulae of these various hormones we find that those hormones with an oxygen atom at C_{11} such as corticosterone *dehydrocorticosterone 17 hydroxy 11 dehydrocorticosterone and 17 hy*droxycorticosterone exercise a marked effect on carbohydrate metabolism [58]

Amorphous Fraction —When the crystalline fractions are removed from whole adrenal cortical extract a highly active residue is left It is claimed that this amorphous fraction exercises no effect on carbohydrate metabolism but is exceedingly potent in its effect on the distribution of electrolytes According to Kendall[8] only one or two micrograms per kilogram of body weight is required to maintain a normal electrolyte pattern in adrenalectomized dogs This is in striking contrast to the relatively large quantities of desoxycorticosterone required to produce the same effect This contrast is particularly significant in view of the fact that desoxycorticosterone is the most potent crystalline fraction of adrenal cortical extract in its effect on electrolyte metabolism Cori and Cori [5] have claimed that the amorphous fraction inhibits the hexokinase reaction

In the light of this review of the adrenal cortical hormones it becomes evident that there is no one fraction which has all the functions of the adrenal cortex In short there is no one vital hormone of the adrenal cortex

The Role of Cholesterol and Ascorbic Acid in Adrenal Cortical Function —It has been known for a considerable time that the stainable lipid of the adrenal cortex decreased under conditions associated with increased cortical secretion and that similar changes occurred in the cholesterol content of the gland Long and his group[76] found that the injection of a highly purified preparation of adrenocorticotropic factor into the rat resulted in a marked decrease in adrenal cholesterol As a matter of fact a single injection of 2 mgm of this hormone caused a 50 per cent reduction in the cholesterol content of the adrenal This decrease occurred within three to six hours after the injection[279] The cholesterol content of the adrenal returned to normal in about twenty four hours This decrease occurs entirely in the cholesterol ester fraction while the free cholesterol remains unaffected Similar results were observed in hypophysectomized rats but the cholesterol content of a variety of other tissues was not affected by these injections These investigators further found that exposure of normal animals to various traumatizing procedures resulted in a similar decrease in adrenal cholesterol but identical procedures did not alter the adrenal cholesterol content in the hypophysectomized animal It is obvious then that these changes are mediated through the action of adrenocorticotropic hormone on the adrenal cortex It does not necessarily follow since the reduction in adrenal cholesterol is associated with an increased secretion of adrenal cortical hormone that the former is concerned in the formation of the latter However it can be shown with the aid of tagged cholesterol that this steroid is concerned in the manufacture of progesterone[278] The chemical structure of progesterone is sufficiently similar to that of the adrenal corticosterones to make it likely that the latter are also formed from cholesterol Further evidence along these lines includes the decrease in ovarian cholesterol following the administration of gonadotropin[277]

Similar observations were made with reference to ascorbic acid The adrenal cortex is unusually rich in ascorbic acid and following the injection of adrenocorticotropic hormone there occurred a sharp drop in the Vitamin C content of this gland This decrease became evident within twenty minutes after the injection and reached a peak within an hour A return to the normal content ensued in twelve hours As with cholesterol exposure of normal animals to various stresses resulted in a marked decrease in adrenal ascorbic acid while similar changes did not occur in the hypophysectomized animal

When the stress is slow in onset and prolonged the change noted is rather an increase in size of the adrenal than any decrease in the adrenal content of cholesterol or ascorbic acid If the stress is continuous and severe there is complete adrenal cortical depletion of cholesterol and ascorbic acid Similarly if adrenocorticotropin is administered over a prolonged period of time the adrenal hypertrophies but its stores of cholesterol and ascorbic acid remain low When recovery ensues following a severe stress the adrenal content of cholesterol and ascorbic acid is depressed for a prolonged

period but returns to normal after several days During this period the adrenal may hypertrophy markedly

Finally, Long[76] emphasized the excellent correlation which exists between the decline in adrenal cholesterol and ascorbic acid and such manifestations of adrenal cortical activity as the increase in liver glycogen in fasting animals and the fall in the number of circulating lymphocytes and eosinophils

The present available evidence would strongly favor the thesis that both cholesterol and ascorbic acid play an important role in the actual manufacture of the adrenal cortical hormones As yet no one has confirmed the claim of Lowenstein and Zwemer[5] as to the isolation of a steroid ascorbic acid compound from the adrenal cortex The possibility that such a compound may exist however, must be entertained It may be wise to mention here that ascorbic acid exercises no significant effect in the adrenalectomized animal or the patient with Addison s disease

The Relation of the Adrenals to the Urinary Excretion of the Neutral 17 Ketosteroids — This problem as well as that dealing with the isolation of androgenic and estrogenic compounds from the adrenal is discussed in further detail in the chapter on *Blood Electrolyte and Hormonal Studies* in adrenal cortical tumors p 352

The term 17 ketosteroids was applied by Callow and his coworkers[86] to those steroids with a ketone group on the 17th carbon atom and a free methylene group These neutral 17 ketosteroids which form the urinary products of androgenic metabolism arise from substances produced by the adrenal glands and male gonads[87 88 89 90 91 92 93] They are the neutral non phenolic fraction and are divided into alpha and beta ketosteroids The terms alpha and beta refer to the position of the 3 hydroxy group The alpha ketosteroids include androsterone and 3 α hydroxyetiocholanone 17 while the beta ketosteroid include dehydroisoandrosterone and isoandrosterone The dehydroisoandrosterone and the isoandrosterone belong to the 3 α hydroxy steroid series and are unsaturated They can therefore be precipitated by digitonin and thus separated from the alpha ketosteroids[94 95] The neutral 17 ketosteroids normally present in male and female urines are androsterone 3 α hydroxyetiocholane 17 one and dehydroisoandrosterone Estrogen is similarly present in normal urines but this substance is a weak phenolic 17 keto steroid Isoandrosterone is encountered in pathologic urines[97] and perhap in normal female urines[98] In addition to these substances $\Delta_{3,5}$ androstadiene 17-one 3 α hydroxy androsten 17 one as well as pregnane 3 17 20 triol have been identified in pathologic urines It is probable that the alpha neutral ketosteroids arise from both the adrenal and gonadal secretions but available evidence indicates that the beta keto teroids are excretion products of the cells of the adrenal cortex only[89 91 93 97 99 100] It should be emphasized that these neutral 17 ketosteroids are by no means the only ketosteroids of this character excreted in the urine Under normal circumstances the alpha fraction constitutes the larger percentage of the total neutral ketosteroids excreted in the urine while the beta fraction constitutes about 10 to 15 percent of the total daily output[101] However in the presence of adrenal cortical tumors there occurs not

only an increase in the total urinary excretion of the neutral 17 ketosteroids but an increase in the percentage of the beta fraction. The increase in the beta fraction attains unusually high levels in the presence of adrenal cortical carcinomata.[101] It is important to observe that androsterone has considerable androgenic activity. This is true to a considerably lesser extent of dehydroisoandrosterone while 3 α hydroxyetiocholanone 17 manifests no such activity.

The daily urinary excretion of total neutral 17 ketosteroids in normal individuals varies somewhat with the sex and considerably with the age of the individual. In general males have a somewhat greater daily urinary excretion of these steroids than do females, and prior to sexual maturity the values for the total daily excretion are quite low. Thus Talbot and his group[101] find that the average daily excretion of total neutral ketosteroids of children under seven years of age was 1.3 mgm. Between seven and twelve years it was 4.0 mgm. and 8.2 mgm. between twelve and fifteen years. Adult men excrete an average of 15.0 mgm. and adult women 10.2 mgm. The range in any one group is quite wide as indicated by Talbot's table.[101]

The daily excretion of neutral 17 ketosteroids is influenced by a variety of pathologic states.[107] Thus it is low in malnutrition, anorexia nervosa, various gastrointestinal disturbances, anemia, infections and in liver disease. It is extremely low, frequently reaching zero levels in Addison's disease and in Simmonds' cachexia. It is increased in adrenal cortical hyperfunction due to hyperplasia and tumors of the adrenal cortex and in Cushing's syndrome. The daily urinary excretion reaches particularly high levels, especially of the beta fraction, in carcinomata of the adrenal cortex.

The Relation of the Adrenals to the Urinary Excretion of Glycogenic Corticoids.—Venning and her coworkers[80, 81] were interested in determining the urinary excretion of those adrenal steroids possessing activity in carbohydrate metabolism. For this purpose they employed a modification of the Reinecke-Kendall test[28] used for the assay of small amounts of corticoids. With this biologic assay technic they measured one type of adrenal cortical function. Neither the group of substances purely active in electrolyte metabolism nor those having androgenic action affect the assay of the glycogenic corticoids. The test is based upon the ability of certain adrenal corticoids to cause a deposition of glycogen in the livers of fasted adrenalectomized mice. The substances which yield this reaction exercise an effect exclusively on carbohydrate and protein metabolism and to the best of our knowledge are derived only from the adrenal cortex. They are labile substances and their degree of destruction or conversion into other compounds *in vivo* is unknown. The urinary excretion of these corticoids in all probability represents only a small fraction of the total amount elaborated in the adrenal gland itself.

The urinary excretion of the glycogenic corticoids does not necessarily parallel the urinary excretion of the neutral 17 ketosteroids both in normal and in pathologic states. The latter are excreted in much larger quantities than the former, milligrams as against micrograms. As with the 17 ketosteroids the excretion of the corticoids is somewhat higher in nor

period but returns to normal after several days. During this period the adrenal may hypertrophy markedly.

Finally, Long[6] emphasized the excellent correlation which exists between the decline in adrenal cholesterol and ascorbic acid and such manifestations of adrenal cortical activity as the increase in liver glycogen in fasting animals and the fall in the number of circulating lymphocytes and eosinophils.

The present available evidence would strongly favor the thesis that both cholesterol and ascorbic acid play an important role in the actual manufacture of the adrenal cortical hormones. As yet no one has confirmed the claim of Lowenstein and Zwemer[85] as to the isolation of a steroid ascorbic acid compound from the adrenal cortex. The possibility that such a compound may exist, however, must be entertained. It may be wise to mention here that ascorbic acid exercises no significant effect in the adrenalectomized animal or the patient with Addison's disease.

The Relation of the Adrenals to the Urinary Excretion of the Neutral 17-Ketosteroids.—This problem, as well as that dealing with the isolation of androgenic and estrogenic compounds from the adrenal, is discussed in further detail in the chapter on "Blood Electrolyte and Hormonal Studies in adrenal cortical tumors," p. 352.

The term "17-ketosteroids" was applied by Callow and his coworkers[86] to those steroids with a ketone group on the 17th carbon atom and a free methylene group. These neutral 17 ketosteroids which form the urinary products of androgenic metabolism arise from substances produced by the adrenal glands and male gonads.[87, 88, 89, 90, 91, 9, 93] They are the neutral non phenolic fraction ,and are divided into alpha and beta ketosteroids. The terms alpha and beta refer to the position of the 3 hydroxy group. The alpha ketosteroids include androsterone and 3 α hydroxy aetiocholanone 17, while the beta ketosteroids include dehydroisoandrosterone and isoandrosterone. The dehydroisoandrosterone and the isoandrosterone belong to the 3 α hydroxysteroid series and are unsaturated. They can therefore be precipitated by digitonin and thus separated from the alpha ketosteroids.[94, 95] The neutral 17 ketosteroids normally present in male and female urines are androsterone, 3 α hydroxy aetiocholane 17-one and dehydroisoandrosterone. Estrogen is similarly present in normal urines, but this substance is a weak phenolic 17 ketosteroid. *Isoandrosterone is encountered in pathologic urines*[9] and perhaps in normal female urines.[98] In addition to these substances $\Delta_{3,5}$ androstadiene-17-one, 3-α hydroxy androsten 17 one, as well as pregnane 3, 17, 20-triol have been identified in pathologic urines. It is probable that the alpha neutral ketosteroids arise from both the adrenal and gonadal secretions, but available evidence indicates that the beta ketosteroids are excretion products of the cells of the adrenal cortex only.[89, 91, 93, 9, 99, 100] It should be emphasized that these neutral 17 ketosteroids are by no means the only ketosteroids of this character excreted in the urine. Under normal circumstances the alpha fraction constitutes the larger percentage of the total neutral ketosteroids excreted in the urine, while the beta fraction constitutes about 10 to 15 percent of the total daily output.[101] However, in the presence of adrenal cortical tumors there occurs not

duced by a polypeptide. This latter compound may contain as little as five amino acids. The original whole adrenocorticotropin has an isoelectric point at pH 4.7 and a molecular weight of 20,000. It contained 46.3 per cent carbon, 5.89 per cent hydrogen, 15.65 per cent nitrogen, and 2.30 per cent sulfur. There was no carbohydrate, phosphorus, or cysteine in the hormone. There was 1.93 per cent methionine and 7.19 cystine. The hormone is readily soluble in water.

Adrenocorticotropin is a powerful inhibitor of growth in the experimental animal. This is easily observed in the epiphyses of young animals subjected to treatment with this hormone. There is noted a decrease in width of the epiphyseal cartilage, retardation of endochondrial bone formation, a decrease in osteoblastic and osteoclastic bone activity, and irregularity of the cartilage columns in the zones being altered to bone. These effects are only observed in the intact animal and not in the adrenalectomized one. Part of this effect of adrenocorticotropin is apparently mediated by inhibition of the effects of growth hormone. The administration of adrenocorticotropin results in a marked increase in urinary nitrogen excretion and a loss of weight in the rat.[55] In addition, certain enzyme systems have been shown to be affected. Liver arginase is increased,[56] and serum alkaline phosphatase is decreased.[57] These last two effects are neutralized by growth hormone.

In addition, the administration of adrenocorticotropin results in a marked delay in wound healing, apparently by preventing the laying down of ground substance and collagen and inhibiting the formation of fibroblasts.

Thymic and lymphatic tissue undergo involution following the administration of this hormone, and the number of circulating lymphocytes, as well as of eosinophils, is considerably decreased. It is possible that in addition to destruction of these hematic cells inhibition of proliferation is also induced.

The administration of adrenocorticotropin results in a marked outpouring of cortical hormones, including those measured as the neutral 17-ketosteroids and urinary corticoids. Suggestive evidence of the activity of the adrenal under the influence of adrenocorticotropin is found in the depletion of adrenal cholesterol and ascorbic acid following the injection of this compound. Recent evidence suggests that compound F is the carbohydrate regulating steroid produced in largest quantity following the administration of ACTH.

The adrenal cortex is known to be an extragonadal source of androgens.[47] It has been demonstrated that the accessory sex organs of castrated guinea pigs respond to beef adrenal implants,[48] and Davidson and Moon[49] produced enlargement of the seminal vesicles and prostate in the castrated rat by the administration of a pituitary extract rich in adrenocorticotropic activity. Li and Evans, however,[50] were unable to stimulate or maintain the secondary sexual organs of castrated rats with a purified fraction.

As do large doses of adrenal cortical steroids,[51] adrenocorticotropin given for a period long enough to produce adrenal cortical hypertrophy results in maintenance of muscle glycogen and hyperglycemia in the fasted animal. In normal rats,[5] the administration of ACTH results in glycosuria, hyperglycemia, a loss of weight, and an increased loss of nitrogen and potassium

mal males than in females. However, although the corticoids are present in only negligible amounts in the newborn infant the urinary excretion rapidly increases and attains normal adult levels after the age of two and one-half years. The general normal adult range for males varies from 40 to 85 glycogenic units per cc. while for females it varies between 25 and 55 units. These values are markedly reduced in Addison's disease and in panhypopituitarism and are only slightly if at all reduced in anorexia nervosa. In Cushing's syndrome they are generally markedly elevated, frequently attaining a value of several hundred. The degree of elevation in the excretion of the urinary corticoids in Cushing's syndrome is apparently unrelated to the character of the adrenal pathology present. Normal values are usually obtained in simple hirsutism.

Physiologic states such as pregnancy, particularly late pregnancy, and muscular exercise are accompanied by an increased excretion of the corticoids. Essentially the same is true following trauma, infection, and surgical procedures. In short, any state associated with an increase in adrenal cortical function will cause an increase in the manufacture and excretion of the glycogenic corticoids.

The activity of the corticoids is expressed in terms of glycogenic units excreted in the urine per twenty-four hours, one glycogenic unit being equivalent to the biologic activity of one microgram of 17-hydroxy-11-dehydrocorticosterone (Compound E of Kendall).

The urinary excretion of the 11-oxyketosteroids as determined by the colorimetric procedure described by Talbot and his group [83] parallels the results obtained with the biologic assay of the glycogenic corticoids. Normal values for urinary 11-oxyketosteroids range between 0.12 and 0.34 mgm. per day. In Addison's disease, hypopituitarism, and in hypothyroidism the values are low. In Cushing's syndrome, adrenal cortical virilism, in patients with severe burns, or following extensive operative procedures the values are elevated.

Another reduction method has been reported by Heard and his co-workers.[254] Their normal values in adults for the daily urinary excretion of these compounds ranged from 1.10 to 2.1 mgm. per twenty-four hours. A method involving periodic oxidation and measurement of the formaldehyde liberated has been employed by several workers.[255, 86] Daughaday and his co-workers [86] found by means of this method that normal individuals excrete 1.0 to 1.6 mgm. per twenty-four hours.

Of interest is the fact that the newborn full-term or premature infant excretes measurable amounts of corticoids. The adrenals in these infants respond to stress and to the administration of adrenocorticotropin and the urinary excretion of corticoids is increased.[87, 88]

Physiologic Effects of Adrenocorticotropin (ACTH).—The recent availability of purified pituitary fractions has enabled us to employ these protein hormones in elucidating the function of the hormone itself and of the end organ it stimulates.

Li and Evans,[250] as well as White and his co-workers [254] have found methods of preparing purified adrenocorticotropin from the pituitaries of sheep and swine. The hormone is a protein although recent work by Li has shown that the metabolic effects of adrenocorticotropin may be pro

has been claimed [73] that the administration of adrenocorticotropin may reduce the basal metabolic rate, at least in patients with hyperthyroidism. In our experience it has caused in addition a fall in the serum protein-bound iodine and an increase in the urinary excretion of I^{131}. The fasting blood sugar may be considerably increased. The glucose tolerance curve may become diabetic in character and glycosuria may ensue. Conn[270] has produced temporary diabetes mellitus in man with this pituitary fraction. Other workers have found only occasional significant disturbances in carbohydrate metabolism.[73]

The administration of adrenocorticotropin is followed by an increase in urinary uric acid and urinary creatine but not in urinary creatinine. Generally no effect on the serum alkaline phosphatase is observed. The serum antihyaluronidase may be decreased and the action of hyaluronidase on tissues in inhibited. Urinary uropepsin is increased but not in the patient with a total gastric resection.

In general, the prolonged administration of adrenocorticotropin may induce all the features of Cushing's syndrome including rounding of the faces, acne, hirsutism, keratosis pilaris, amenorrhea, hypochloremic alkalosis, striae, hypertension, depression or euphoria, and muscular weakness. The question of antihormone formation following the use of ACTH is a very interesting one. Unlike what prevails following the prolonged administration of gonadotropic or thyrotropic factors, the prolonged use of ACTH only infrequently results in the formation of antihormone.[59] The explanation for this difference in behavior between these pituitary fractions is unknown. The lack of antihormone formation following the use of ACTH may be related to the relative purity of this fraction or perhaps to the relatively small size of its molecule.

The Clinical Uses of ACTH and Cortisone.—The therapeutic effects of cortisone and ACTH are essentially similar, although in most instances in which comparable studies were conducted ACTH seemed to be somewhat more prompt in its effect. This may not be true in all cases, but in our experience has been so in acute disseminated lupus erythematosis, polyarteritis and in the leukemias. It has been difficult to assay experimentally the comparative effects of the two hormones. In our laboratory we found [9, 96] that 12.5 mgm. of ACTH will uniformly inhibit the provocative phase of the Shwartzman phenomenon while 40 mgm. of 17-hydroxy-11-dehydrocorticosterone or Compound E or cortisone will inhibit the phenomenon in only half the experimental animals. This of course means only that ACTH is more effective milligram for milligram in this limited area and by no means necessarily applies to the entire spectrum of metabolic effects. Cumulative experimental and clinical experience however tends to indicate that the general effectiveness of ACTH as compared with cortisone is probably of the ratio of 2:1 to 4:1. This may mean that 100 mgm. of ACTH, for example, is more promptly effective than 100 mgm. of cortisone because the former when injected parenterally liberates more than 100 mgm. of cortisone from the intact adrenal, or it may mean that ACTH results in the elaboration of other adrenal cortical fractions in addition to Compound F, which exercise therapeutic and metabolic effects. That the latter unquestionably occurs is evidenced by the fact that the

Furthermore, alloxan induced diabetes in rats is intensified following the use of this compound [5]

The administration of adrenocorticotropin results in a marked fall in both the ascorbic acid and cholesterol content of the adrenal in the rat and in the guinea pig. The former returns to its normal concentration in twelve hours, the latter in twenty four hours. Prolonged administration of this hypophyseal compound keeps the adrenal depleted of cholesterol and ascorbic acid and hypertrophy of the cortex is observed. It has been postulated that cholesterol is the precursor of the adrenal cortical hormones and that ascorbic acid is involved in some way with the mechanism. Lowenstein and Zwemer [58] have claimed to have isolated a steroid containing a molecule of ascorbic acid from the adrenal cortex. Their claim, however, has not as yet been confirmed.

Administration of adrenocorticotropin to the human subject has resulted in changes similar for the most part to those noted in the experimental animal [63, 64, 6, 66, 67, 271, 73, 74]. It is obvious, of course, that inasmuch as adrenocorticotropin in stimulating the adrenal will result in the production of many steroids of varied activity, the physiologic actions of this drug might differ in some respects from those of Compound E (17-hydroxy-11-dehydrocorticosterone or cortisone).

Following the administration of adrenocorticotropin 50 to 200 mgm a day given in divided doses every six hours, there is noted a marked increase in the urinary excretion of the neutral 17 ketosteroids as well as the 11-oxycorticoids. There is a considerable leukocytosis and neutrophilia with a decrease in the absolute number of circulating lymphocytes and eosinophils. Sodium and chloride are retained at least temporarily and there is an associated gain in weight, hemodilution and at times edema. The blood pressure may rise markedly although in most instances no effect is noted. There is frequently a diuresis of potassium concomitant with the retention of sodium. If the loss of potassium and chloride is great enough an alkalosis is noted. This effect may be intensified by the injection of mercuhydrin [9]. The electrolyte pattern of the serum when this alkalosis occurs is that reported by McQuarrie and others in Cushing's syndrome and is characterized by an elevated serum sodium and bicarbonate and a low serum chloride and potassium [68]. This pattern we know from the work of Darrow [93] is a reflection in part of the depletion of the potassium store of the body and may be corrected by the administration of potassium. Nitrogen wastage in the urine is induced. There is often noted an outpouring of calcium and with it phosphorus chiefly in the feces. The serum levels of calcium and phosphorus however remain unaltered [68, 4]. The level of the serum cholesterol may fall slightly but the cholesterol ester is markedly reduced according to Conn. With prolonged therapy, however, there occurs a considerable increase in both the serum cholesterol and the total lipids [271]. Other investigators have not confirmed these observations. The urinary excretion of estrogen may be unchanged or slightly increased. Although sufficient data is as yet unavailable there is evidence to suggest that the urinary excretion of gonadotropin may be altered. We have found an increase in the urinary excretion of gonadotropin following the administration of both cortisone and ACTH [94]. It

lation such as follows the use of ACTH or by adrenal cortical substitutive therapy such as occurs with cortisone

The available evidence to date would indicate that although ACTH and cortisone are capable of ameliorating the disease states enumerated no actual cure results from their administration In most of the illnesses cited ACTH was used in a dosage of approximately 100 mgm a day divided equally every six hours Cortisone which is more slowly absorbed is generally employed in larger doses varying from 100 to 300 mgm a day given in two to four divided doses When used orally cortisone is administered in slightly larger amounts and divided into 3 or 4 equal daily doses The prolonged use of these agents is not without considerable hazard due to their metabolic effects The occurrence of hypertension edema and congestive failure must be carefully watched for Hyperglycemia and glycosuria occur infrequently but are more prone to be manifest in patients with a family history of diabetes mellitus Rounding of the facies acne amenorrhea and the development of violaceous striae over the flanks are frequently observed It is evident that the prolonged administration of ACTH and cortisone may result in a picture which simulates spontaneous Cushing's syndrome Hirsutism occurs commonly in the female and a diffuse pigmentation due to the deposition of melanin in the skin is not infrequently observed The use of cortisone and ACTH is often associated with the development of mental symptoms the most characteristic of which is a pronounced euphoria Depression and elation however are occasionally noted particularly in patients who prior to treatment manifested latent evidences of manic-depressive psychoses Electroencephalographic studies following the use of ACTH reported by Hoefer and Glaser [80] often show a reduction in amplitude regularity and continuity and a slowing of the basic alpha activity as well as the appearance of large amounts of slow activity which occurred at random or in bursts and which was often increased in incidence or amplitude or both in response to overventilation These changes which generally occurred in three to five days after the beginning of therapy usually subsided within a week after discontinuation of the drug Diffuse epileptiform convulsions have been noted in 4 out of 17 patients with acute disseminated lupus erythematosus treated with ACTH and cortisone in our clinic

BIBLIOGRAPHY —*See pages 219–230*

parenteral administration of ACTH results in the increased urinary excretion of 17 hydroxy-corticosterone or Compound F which exercises effects similar to those of Compound E Finally, whereas ACTH is readily soluble in distilled water and normal saline Compound E is available only in suspension and hence the rate of absorption of this fraction may be much slower than that of ACTH Cortisone is effective orally and the metabolic and clinical effects following its oral administration occur as promptly as with the parenteral administration of ACTH Anaphylactic shock may be prevented by the use of cortisone or ACTH although neither agent has been demonstrated to increase antibody formation

In 1948 our group [90] reported the clinical use of ACTH in a patient with myasthenia gravis with a thymic tumor Following the administration of 40 mgm of ACTH daily given in 4 divided doses over a four day period there occurred a marked shrinkage of the tumor and an improvement of the symptoms of myasthenia gravis This was the first demonstration of the therapeutic effectiveness of this compound in disease The observation of the shrinkage of the thymic tumor which followed the administration of ACTH in this case laid the groundwork for the use of this agent in the treatment of lymphatic tumors This paper was shortly followed by the reports of Conn and his coworkers, [18] Hellman [298] and Wolfson [299] on the use of ACTH in the treatment of gout In April 1949 Hench and his coworkers reported on the brilliant results obtained in patients with rheumatoid arthritis following the use of cortisone and ACTH [259] The publication of these various papers was followed by extensive study of the effects of these hormonal agents in a large variety of illnesses At a conference on ACTH under the direction of Dr John R Mote of the Armour Laboratories held in Chicago in October 1949 and again in December 1950 the clinical spectrum of the therapeutic effectiveness of this agent was surveyed [73] It was found to be therapeutically efficacious to varying degrees in a large number of disorders, which included spontaneous hypoglycemia, gout some hypertensive states nephrosis and acute nephritis lymphoid tumors acute and chronic lymphatic leukemias rheumatoid arthritis, Still s disease rheumatic carditis dermatomyositis periarteritis nodosa, scleroderma diseases of collagen such as acute disseminated lupus erythematosis, ulcerative colitis hypersensitive and allergic states—particularly status asthmaticus unresponsive to other forms of therapy pneumococcal and atypical virus pneumonia myasthenia gravis and eosinophilic disease

This is an impressive and widely dispersed list of illnesses in which cortisone and ACTH are effective These illnesses are however in no way related to primary adrenal cortical disease Studies of adrenal cortical function conducted on most patients by other investigators and in our own laboratory prior to the advent of therapy showed no primary adrenal cortical defects, other than perhaps some adrenal cortical exhaustion such as would occur in illnesses of prolonged duration The therapeutic responses obtained in this wide range of disease would indicate, therefore that the adrenal cortex participates significantly in the defense mechanism of the body whenever it is threatened by any pathologic state The defense response can be heightened either by further adrenal cortical stimu

renocorticotropic factor of the anterior pituitary lobe will cause an increase in size and activity of the adrenal cortex of both the normal and the hypophysectomized animal.[103, 104, 106] This has its human counterpart in patients with Simmonds' cachexia who manifest considerable atrophy of the adrenal cortex.

Such hormonal agents as thyroxine and estrogens fail to induce adrenal cortical hypertrophy in the hypophysectomized animal,[103, 106, 107] while their effects are quite pronounced in the intact animal. This is essentially true of the compensatory hypertrophy of the remaining adrenal following unilateral adrenalectomy.

Tepperman and Engel[107] have emphasized the significance of protein catabolism in adrenal size, and this factor probably plays an important role in adrenal cortical hypertrophy observed in starvation, cachexia associated with neoplasm, burns, and a variety of other states in which extensive protein breakdown occurs. The adrenal cortex is intimately concerned with protein and carbohydrate metabolism, and, as discussed elsewhere in this chapter (page 188), certain adrenal cortical fractions will increase protein catabolism and gluconeogenesis. Where there is a sudden increase in available protein either through an exogenous or through an endogenous source there will be a corresponding increase both in adrenal cortical function and size.

The mechanism or mechanisms implicit in the production of adrenal cortical hypertrophy by the various agents is by no means clear, but the significance of the anterior pituitary, and perhaps more specifically the action of the adrenocorticotropic factor in such a relationship is clear. It is difficult to know whether the effect of protein metabolism is mediated through the hypophysis or whether its effect is essentially autonomous and entirely independent of the pituitary. There is some evidence to indicate that its effect is regulated through affecting the balance between the growth hormone of the anterior pituitary lobe, which enhances protein anabolism, and the adrenocorticotropic factor, which stimulates protein catabolism.[107]

A decrease in the size of the adrenal cortex will occur as a result of the following factors:[107]

1. Hypophysectomy
2. The continued use of testosterone
3. The presence of a persistent and actively functioning thymus
4. The use of progesterone (in the male rat)
5. The use of whole cortical extract or desoxycorticosterone
6. The prolonged administration of cortisone

Of particular interest is the effect of whole adrenal cortical extract and desoxycorticosterone on adrenal cortical size. Ingle and his group[108] and Wells and Kendall[109] have demonstrated the adrenal cortical atrophy which follows the continued injection of cortical extract into the normal animal. Sarason[110] has further elaborated on this point and shown that following hypophysectomy the injection of desoxycorticosterone results in an even more marked degree of atrophy of the adrenal cortex than is observed either with hypophysectomy or desoxycorticosterone alone.

These observations would emphasize that the atrophic changes following the administration of the cortical extracts are mediated through a suppres

Chapter 8

PHYSIOLOGY OF THE ADRENAL CORTEX (*Cont.*)

FACTORS DETERMINING ADRENAL SIZE. RELATION OF ADRENAL CORTEX TO OTHER ENDOCRINE GLANDS. RELATION OF ADRENAL CORTEX TO SHOCK

THE RELATIONSHIP OF THE ADRENALS TO THE OTHER ENDOCRINE GLANDS

Physiologic and Pathologic Factors Influencing Adrenal Size and Function. — The circumstances under which the size of the adrenals may be altered are not only of considerable physiologic interest but are of great clinical significance. Tepperman and Engel[10] have reviewed this subject comprehensively and have enumerated and discussed many of the responsible factors.

There are a large variety of agents both physiologic and pathologic which may induce adrenal cortical hypertrophy.

Endocrinologic Factors

1. Adrenotropic factor of the anterior lobe of the pituitary
2. Thyroxin
3. Estrogens
4. Castration in the male
5. Insulin

Pathologic Factors

1. Increased protein catabolism
2. Complete inanition
3. Shock
4. Burns
5. Anorexia
6. Acute and chronic infections
7. Tumors associated with cachexia
8. Vitamins B and C deficiency states
9. Unilateral adrenalectomy

Miscellaneous Factors

1. Exercise
2. High protein diets
3. Late pregnancy and puerperium
4. Injection of cholesterol or high cholesterol diets
5. Various noxious agents (cold, morphine, adrenalin, *etc.*) including the so-called alarm reaction

The functional status of the anterior pituitary is probably the most important endocrinologic factor in determining adrenal size. Indeed, it acts as the key agent through which the other hormonal substances exercise their effect on the adrenal. It is now well established that hypophysectomy is followed by adrenal cortical atrophy, while the administration of the ad-

mal is capable of survival for prolonged periods while the untreated bilaterally adrenalectomized one succumbs within a few days

These points are not made to detract from the importance of the pituitary gland and indeed there is ample evidence to support the concept that this gland is probably the key one in the endocrinologic system of balance But we will lose sight of an important physiologic fact if we fail to appreciate the influences of the other glands particularly the adrenal cortex on the hypophysis Certainly the fact that survival without the pituitary is possible points to some degree of autonomy and independence on the part of the remaining endocrine organs

We can approach the problem of the relationship of the adrenals to the hypophysis by observing the effect of the latter on certain specific functions as well as on the histology of the former Let us note then the effect of hypophysectomy on the histology of the adrenals and the anatomic influence of adrenalectomy on the anterior lobe of the hypophysis Similarly there is considerable experimental data dealing with the effect of the pituitary on such specific adrenal cortical functions as salt and water metabolism carbohydrate and protein metabolism resistance to stress *etc*

The Influence of the Pituitary Gland on the Anatomy and Histology of the Adrenal Cortex —It has been definitely established that total hypophysectomy results in a rapid atrophy of the adrenal cortex in a variety of animals including the dog[104, 105] The atrophy is limited to the cortex the medulla apparently remaining unaffected[11, 111] The cells of all three zones of the cortex show a diminution in the amount of cytoplasm The atrophic process begins in the reticular zone and eventually involves the fascicular layer and finally the entire cortex When the process is complete the cells are small and distorted the reticular layer is unrecognizable while the fascicular layer has completely lost its cord like arrangement of cells In addition the Golgi apparatus has shrunken and the lipoid granules have practically disappeared except from the middle portion of the cortex where some are still present These atrophic adrenals can be almost completely restored to their normal histology by daily homotransplants of the pituitary gland[11] or by the use of suitable pituitary extracts[103, 104, 116, 117] In the rat however the zona glomerulosa is capable of independent function and does not undergo atrophy following hypophysectomy[15]

Similar adrenal cortical changes have been noted clinically in patients with pituitary deficiency diseases such as pituitary dwarfism Simmonds cachexia and in anencephaly[114]

Certain clinical and experimental hyperpituitary states are conversely associated with hypertrophy of the adrenal cortex Thus the adrenals in acromegaly are characterized not only by hyperplasia of the cortical cells but frequently actual adenomata of the adrenal cortex are encountered[11] Experimentally adrenal cortical hypertrophy has been induced in both the intact and the hypophysectomized animal by treatment with the adrenocorticotropic factor of the anterior pituitary lobe[103, 104, 116, 117]

One further point of interest is the relationship between the pituitary and the compensatory hypertrophy of the remaining adrenal in the unilateral adrenalectomized animal In the intact animal the removal of one adrenal is promptly followed by a compensatory increase in size of the cor-

sing effect on the pituitary. That is, that excess available adrenal cortical extract decreases the adrenocorticotropic hormone secretion of the anterior pituitary, which in turn causes atrophy of the adrenal cortex.[108,109,110] Essentially the same is true following the prolonged use of cortisone. This latter compound inhibits the secretion of adrenocorticotropic hormone more readily than do either whole adrenal cortical extract or desoxycorticosterone.

The data outlined above present in a rather brief fashion the effects of various physiologic factors and pharmacologic agents on adrenal size and we must assume on adrenal function since there appears to be a correlation *between gland mass and rate of hormone secretion*. It is equally interesting to attempt to determine the influence of various pathologic states on adrenal cortical histology and an extensive literature dealing with this field has developed.

Sarason[111] studied the morphologic changes in the adrenals of 110 patients who died of various causes unrelated to primary adrenal disease. Twenty-eight patients of this group died of either an acute or a chronic inflammatory state. In 26 members of this group there was moderate to marked enlargement of the adrenal cortex and all the members of the series showed a depletion of lipoid content of the cortex. In many there was an alteration in the distribution of the cortical lipoids in that the lipoid-containing cells were now in the inner instead of the outer part of the zona fasciculata. Thirteen cases were instances of malignant neoplasm. All showed an increase in adrenal cortical size and some degree of lipoid depletion. It is of interest that the degree of adrenal cortical hypertrophy and lipoid depletion was considerably greater in the patients with cachexia than in those who failed to show this symptom. Patients with hypertension also showed adrenal cortical hypertrophy but in contrast to the other groups an increase in the amount of cortical cell lipoids.

It should be noted that most pathologic states are associated with an increase in adrenal cortical size and that with the exception of certain endocrinologic abnormalities (Simmonds' disease, status thymicolymphaticus, myxedema) adrenal cortical hypoplasia as a response to systemic disease is relatively unknown. It is reasonable to assume that the increase in cortical size as a response to the impact of systemic trauma represents a compensatory and protective mechanism.

The Relation of the Adrenals to the Pituitary Gland.—The physiology of the adrenal cortex is intimately concerned with that of the anterior lobe of the pituitary body. The relationship is unquestionably a mutually interdependent one as evidenced by the fact that destruction of the anterior hypophysis results in adrenal cortical atrophy while adrenal cortical disease induces morphologic alterations in the pituitary. In two patients of our group who succumbed to Addison's disease due to tuberculosis of the adrenals there was associated atrophy of the anterior hypophysis. Similarly, in instances of adrenal cortical carcinoma extensive histologic alterations in the anterior pituitary have frequently been noted. In view of the specific nature of the adrenal disease in the cases cited it is a justifiable assumption that the pituitary changes were secondary to the adrenal disturbance. It is not without significance that the hypophysectomized ani

mal is capable of survival for prolonged periods while the untreated bilaterally adrenalectomized one succumbs within a few days

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tex of the remaining adrenal. This phenomenon does not occur in the hypophysectomized animal. However, if adrenocorticotropic hormone is administered to such an animal the usual hypertrophy of the remaining adrenal will ensue.

The Influence of the Adrenals on the Anatomy and Histology of the Anterior Lobe of the Hypophysis.—Primary clinical disease of the adrenal, and experimental adrenalectomy induce fairly consistent changes in the histology of the anterior hypophysis. In Addison's disease there may be complete atrophy of the anterior pituitary lobe as occurred in 2 instances in our group. More commonly there is a diminution in the number of normal basophils. These elements become smaller in size, lose their granular appearance, and become irregular and indistinct in outline. Similarly the eosinophils may become atrophic and pyknotic, but apparently the major changes occurs in the basophilic elements. In addition to these cellular changes there is an increase in vascularity of the pituitary due to dilatation of its capillaries. Similar changes have been reported in the bilaterally adrenalectomized dog.[108] Hyalinization of the cytoplasmic granules of the basophils of the adenohypophyses or the so-called Crooke's changes are observed in patients with adrenal cortical hyperfunction manifesting Cushing's syndrome. Identical changes have been reported on postmortem examination in patients with a variety of unrelated illness treated with cortisone.[109]

The Effect of the Pituitary on Various Metabolic Functions Related to the Adrenal Cortex.—Acute adrenal insufficiency both in the experimental animal and in the patient with Addison's disease is characterized by a profound disturbance in the electrolyte and water balance, the nature of which is discussed elsewhere in this book. The control of the salt and water metabolism which is essential to life is one of the primary functions of the adrenal cortex. The fact that the hypophysectomized animal is capable of living for a prolonged period of time, in contrast to the adrenalectomized animal, is in itself indicative of the lack of influence which the pituitary exercises on this particular adrenal cortical function. Following hypophysectomy no change in the blood sodium, chloride, or potassium level occurs.[110] Bilateral adrenalectomy in such an animal, however, is followed by the typical clinical and laboratory evidences of adrenal insufficiency, and death ensues within the usual period of time.

It would seem then that the formation of those adrenal cortical fractions dealing with electrolyte metabolism continues independently of the anterior lobe of the pituitary. It is possible that the latter gland exercises some slight effect on this function as shown by the fact that neither the adrenalectomized nor the hypophysectomized animal is capable of excreting intraperitoneally injected water properly.[118,119] In both types of animals this defect is promptly corrected by the use of adrenal cortical extract.[11]

It is interesting to observe the species differences which occur in this respect. The statements cited above apply to most forms of life with the exception of fowl. In this group the fatal outcome following hypophysectomy can be prevented by the administration of adrenal cortical hormone.[110] In the rat the zona glomerulosa, which apparently is the site of formation of the hormone regulating salt and water metabolism, is

autonomous This region does not atrophy following hypophysectomy nor hypertrophy following the administration of adrenocorticotropin In the human however the situation is somewhat different since the administration of adrenocorticotropin is usually followed by a retention of sodium and chloride

The influence of the pituitary on the carbohydrate functions of the adrenal cortex are of a much more profound character The experimental work of Houssay and of Long and his coworkers[46] has illuminated this field considerably These observers have noted that following hypophysectomy there occurs a rapid depletion of the carbohydrate stores of the fasting rat which is promptly followed by hypoglycemic levels of the blood sugar Following the administration of cortical extract to these animals the glycogen content of the liver is replenished and the blood sugar is restored to normal levels The results of treatment with cortical extract are thus not dissimilar in these experiments to those obtained following the use of anterior pituitary extract The difference between the two lies perhaps in their respective effects on muscle glycogen in that the adrenal cortical hormone is not as capable of inducing and maintaining as high a level of muscle glycogen as is the pituitary hormone

Anterior pituitary extract exercises a diabetogenic effect on the hypophysectomized-depancreatized animal and Long and Lukens[60] have suggested that this effect may at least in part be mediated through the adrenal cortex In support of this hypothesis Lukens and Dohan[1 0] have demonstrated an increase in the glycosuria urinary nitrogen excretion and blood sugar level following the administration of cortical extract to hypophysectomized-depancreatized animals This problem was approached in a somewhat different fashion by Houssay and Biasotti[1 1] who found that if adrenalectomized-depancreatized dogs are treated with adequate amounts of cortical extract the blood sugar level is increased However if in addition anterior pituitary extract is administered there occurs a further considerable elevation of the blood sugar level It is interesting that no exacerbation of the diabetes occurred in such animals following the administration of anterior pituitary extracts alone[1??]

Finally the close similarity in behavior between the adrenal cortex and the anterior lobe of the hypophysis on carbohydrate metabolism is evidenced by the amelioration of total pancreatic diabetes by both hypophysectomy[1 3] and bilateral adrenalectomy[1 0] However despite many similarities there are considerable differences in the behavior pattern of the two glands in respect to carbohydrate metabolism The various experimental observations would suggest that the anterior pituitary lobe influences carbohydrate metabolism through at least two channels (*a*) through the stimulating action of the adrenocorticotropic hormone on the adrenal cortex and (*b*) through another factor or factors one of which is growth hormone which may act directly on the tissues[46] Long[46] suggests that even in relationship to this latter factor some adrenal cortical hormone is necessary for the anterior pituitary effect The observations of Russell[1 4] on the synergism between anterior pituitary extract and adrenal cortical hormone is significant in the light of these observations

In contrast to the interrelationship existing between the pituitary and the adrenal cortex in reference to carbohydrate and protein metabolism no such relationship exists apparently with respect to growth One of the most striking abnormalities of the hypophysectomized animal is the cessation of growth which follows the operation To a somewhat less dramatic extent the same is true following bilateral adrenalectomy of the growing rat In each instance growth is resumed following the use of suitable extracts adrenal cortical extract in the case of the adrenalectomized animal and the growth fraction of the anterior pituitary lobe in the hypophysectomized one[105] In the latter animal the use of homotransplants is equally effective[11] However the use of adrenal cortical extract exercises no effect on the growth curve of the hypophysectomized animal[105,115,116] while pituitary homotransplants exerted an equally negative effect on the bilaterally adrenalectomized rat[105] Indeed in many ways the effects of growth hormone are the antithesis of those observed with adrenocorticotropin The administration of the former results in a positive nitrogen balance a decrease in liver arginase and an increase in serum alkaline phosphatase which is opposite to the effects obtained with adrenocorticotropin[50]

Swann[110] in his excellent review on the pituitary adrenocortical relationship summarizes this relationship quite well He emphasizes that the control exerted by the pituitary over the adrenal cortex is quite marked in respect to carbohydrate protein and fat metabolism while it is less pronounced in influencing the ability of the adrenalectomized animal to resist various stresses trauma and intoxications The effect of the pituitary on the salt and water function of the adrenal cortex is practically nil or at best very minimal while there seems to be no effect exerted by either gland on the other in respect to growth Some evidence has been adduced to indicate a possible interrelationship concerning both muscle metabolism and reproduction However this is by no means clearly established as yet

The Relationship of the Adrenals to the Gonads —The clinical recognition of adrenal cortical tumors and hyperplasia as a cause of virilizing and feminizing syndromes further emphasized the question concerning the relationship between the gonads and the adrenals That such a relationship exists at least in pathologic states is evident from these clinical observations and further highlighted by the similarities in the virilizing syndromes produced by interstitial cell tumors of the testes arrhenoblastomas of the ovary and the adrenal cortical hyperfunctional states These clinical similarities are so striking as to lead inevitably to the conclusion of the existence of some factor or factors common to both the adrenals and the gonads The existence of some interplay between the gonads and adrenals is further exemplified by the functional and anatomic changes in the reproductive system which follow adrenalectomy[11] In Addison s disease in the female as well as in the bilaterally adrenalectomized female animal cessation of menses and estrus often occurs and the ovaries and uterus become small and hypoplastic Similarly in the male there is impotence associated with atrophic changes in the testes and reduction in the size of the prostate However as to whether such a relationship exists under

normal circumstances and is operative physiologically is less easily demonstrable of proof. A large body of literature, a good deal of it confusing and contradictory, has accumulated dealing with the interplay between the adrenals and the gonads. It is not the purpose of the author to become involved in such a controversial discussion but rather to limit the presentation to these facts which are well established and which may serve as a possible springboard for further investigation.

Anatomic Changes in the Adrenals Following Castration.—It is generally agreed that in the male animal castration is followed by adrenal cortical hypertrophy.[117, 128, 129, 130] This hypertrophy is due essentially to an increase in the size of the fasciculate and reticular zones and such hypertrophy may be inhibited by the administration of male sex hormones.[117] In addition, in the immature male mouse castration is followed by hypertrophy of the X zone, although the significance of this change is obscure. Such uniformity of results has not been obtained following castration in the female animal. Most authors, however, agree that following bilateral oophorectomy there occurs a decrease in adrenal size.[129, 131] The disparity of result obtained has probably been correctly explained by Hashimoto[133] who pointed out that the response depends on the age of the animal when the ovariectomy is performed and the time interval that has elapsed after the operation when the adrenals are examined. In immature as well as in mature rats hypertrophy of the adrenals may take place for a matter of several weeks after the operation to be followed by progressive atrophic changes.

The Effect of Estrogens and Androgens on Adrenal Size.—Administration of estrogenic compounds almost uniformly causes marked hypertrophy of the adrenals. The hypertrophy is more pronounced when moderate doses are employed than when excessive amounts are used.[134] The only exceptions to these results are those reported by Clausen and Freudenberger[135] and Selye and Albert[136] who found that in immature normal and castrated rats estrogens cause a decrease in adrenal size. In the hypophysectomized animal, the estrogens are incapable of inducing adrenal cortical hypertrophy even when adrenocorticotropic hormone of the anterior pituitary lobe is administered in adequate amounts to prevent the usual post hypophysectomy adrenal cortical atrophy.[106, 107, 137] Similarly, such hypertrophy may be prevented in the intact animal if testosterone is administered simultaneously with the estrogen.[138] Where other factors which normally would produce an increase in the size of the adrenals are operative, the administration of estrogens will cause an even further increase in adrenal size. Thus Golla and Reiss[107] found that under such circumstances the degree of adrenal cortical hypertrophy was apparently four times as great as that observed without the supplementary use of estrogens.

Androgens, on the other hand, either exercise no effect at all on adrenal size or actually produce atrophy. This is true in both the male and the female animals.[10] Progesterone, similarly, when administered in large amounts produces considerable atrophy of the adrenal cortex.[139]

The Relation of the Adrenal Cortex to the Formation of Sex Hormones and Their Cortin Like Effects.—In another chapter (p. 352) in this book are discussed in detail those hormones elaborated by the adrenal cortex

which manifest estrogenic and androgenic activity In brief, the following compounds having some androgenic and estrogenic properties have been isolated from the adrenal cortex adrenosterone 11 hydroxyisoandrosterone 17 hydroxyprogesterone and estrone These compounds are present in minute quantities only However, this is not necessarily an index of the amount actually formed but may simply be indicative of the amount stored in the gland itself It is significant that the urine of both the castrated male and the ovariectomized female have slight but definite androgenic and estrogenic activity [140]

The sex hormones on the other hand have some cortin like effect which is quite pronounced in the case of progesterone Thus Thorn and Engel[141] have demonstrated that testosterone estrone estradiole and progesterone when injected into the normal dog caused a decreased urinary excretion of sodium and chloride and a slight increase in potassium excretion In addition in the non adrenalectomized and non hypophysectomized animal the estrogens exercise an effect on carbohydrate metabolism similar to that of adrenal cortical extract in that they cause an increased nitrogen excretion and an increase in the liver glycogen nitrogen and weight [142 143 144] With the exception of progesterone none of the other sex hormones exercises enough of a cortin like effect to prolong the life of adrenalectomized animals Gaunt and his coworkers however have demonstrated that bilaterally adrenalectomized ferrets and rats may be maintained in excellent condition with the use of progesterone [145 146]

On the basis of the available experimental and clinical data it is difficult to avoid the conclusion that there is a fairly close functional relationship between the gonads and the adrenals In part this relationship is merely expressive of a common mediative factor *i e* the anterior hypophysis but in addition there appears to be a specific and autonomous adrenocortical gonadal system

The Relation Between the Adrenal Cortex and the Thyroid Gland — The endocrine system is such a delicately poised one and the influence of the hypophysis on all the endocrine glands is so extensive that it is difficult to establish any limited and specific relationship between the various glands This is particularly true of the adrenal cortex and the thyroid Despite a large body of experimental data our actual knowledge of this interdependence is confusing and at best meager In a general sense we know that the patient with Addison s disease usually has a somewhat lowered basal metabolic rate Similarly an occasional patient with hyperthyroidism will manifest a marked and diffuse pigmentation identical with that observed in Addison s disease Examination of the thyroid of patients who have died of adrenal cortical destruction will occasionally reveal extensive atrophic and fibrotic changes This is particularly true where the Addison s disease is due to bilateral adrenal cortical atrophy and the question always arises as to whether both changes may not be due to some common underlying disease process in which *all* the glands are involved In general however the thyroid of such patients or of the bilaterally adrenalectomized animal, does not reveal any particularly striking changes There may be some decrease in the size of the gland and there often is some lymphocytic and plasma cell infiltration Similarly thyroidectomy does

not result in any constant change in the gross anatomy or histology of the adrenals.[147] The paucity of anatomic change however does not necessarily bespeak an absence of functional relationship between the two glands.

Marine[148] has suggested that there exists an antagonistic relationship between the adrenal cortex and the thyroid. This hypothesis was based essentially on the experimental observation that sublethal injury to the adrenals results in a definite and persistent increase in metabolism. This suggested the clinical possibility that hyperthyroidism may be due to dysfunction of the adrenals. When a potent adrenal cortical extract became available treatment with such extract and with fresh adrenal tissue failed to influence the course of the hyperthyroidism.[149] However, the administration of thyroxin or of thyroid extract to the patient with Addison's disease usually exercises an unfavorable effect on the course of the illness. Careful blood electrolyte and balance studies conducted in our laboratory on patients with hyperthyroidism failed to reveal any abnormalities reminiscent of those observed in clinical and experimental adrenal insufficiency. This was true of the pigmented as well as of the non pigmented patient with Graves' disease. However, Koehlche and Kendall[150] have demonstrated that the administration of adrenal cortical extract to dogs rendered hyperthyroid with injections of thyroxin resulted in a decrease in the urinary nitrogen excretion. This would suggest the existence of some compensatory relationship between the adrenal cortex and the thyroid.

As mentioned previously, the thyroid plays some role in adrenal cortical hypertrophy. Thus the administration of thyroxin to the experimental animal results in a considerable increase in adrenal cortical size. As a matter of fact, the question arose at one time as to whether the adrenocorticotropic effect observed with anterior pituitary extract was not a specific function of the thyroid and was actually mediated through that organ. As evidence of this, several observers have failed to obtain adrenal cortical hypertrophy with injections of anterior pituitary extract in the thyroidectomized animal.[151,152] Others, however, were able to induce such hypertrophy in the thyroidectomized animal.[104,153,154,155] The subsequent demonstration that thyroxin will not induce adrenal cortical hypertrophy in the hypophysectomized animal[110,155,156] clarifies the role that the thyroid plays in this phenomenon and establishes the fact that it is mediated through the hypophysis.

In our laboratory we have demonstrated that in the intact animal the administration of epinephrine will result in a decreased uptake of radioactive iodine by the thyroid. In the adrenalectomized rat, however, the administration of epinephrine induces an increased uptake of iodine by the thyroid gland. However, if 17-hydroxy-11-dehydrocorticosterone is given simultaneously with the epinephrine to the adrenalectomized animal, a decreased uptake of radioactive iodine is noted as compared to the uptake in adrenalectomized controls. This would suggest that both the adrenal medulla and cortex play significant roles in thyroid function.[233,234]

The Thymus-Adrenal Relationship.—Patients with Addison's disease not infrequently show a diffuse lymphoid hyperplasia at autopsy. There is often a considerable enlargement of the intra-abdominal lymph nodes and infiltration of many organs with lymphocytes. In children who die of

sudden bilateral massive adrenal hemorrhage (Waterhouse Friderichsen syndrome) not only does one find extensive lymphoid hyperplasia but on many occasions the thymus has been reported to be unduly enlarged

The exact significance of this relationship is by no means clear, but the experimental evidence adduced to date would suggest the possible existence of an antagnostic mechanism operating between the adrenals and the thymus As early as 1909 Soli[157] observed that a slight although definite adrenal hypertrophy follows thymectomy in the experimental animal This observation was subsequently amply confirmed and indeed Gershon Cohen and his coworkers[158] found that the adrenals of young male rats were consistently enlarged following atrophy of the thymus induced by irradiation

The clinical antithesis of this observation was first called to attention by Pappenheimer[159] who pointed out that an enlarged or persistent thymus is frequently found associated with the atrophy of the adrenals in Addison s disease Marine[160] noted that the autopsy of patients who died suddenly of so-called status thymicolymphaticus often revealed an enlarged thymus and hypoplastic adrenals

Some of these results could be reproduced experimentally Jaffe[161] Marine and his group[162] and Kitagawa[163] reported that bilateral adrenalectomy results in thymic enlargement in the immature experimental animal Rowntree[164] found that hypoplasia of the adrenal in the rat could be induced by the administration of thymus extract

This problem was approached in still another fashion Andersen[165] reported that excessive muscular exercise in the rat induced enlargement of the adrenals and marked atrophy of the thymus Selye[166] confirmed this observation but pointed out that it was part of the phenomenon of the "alarm reaction" and could be induced by a variety of noxious agents He significantly demonstrated however that the thymic changes could be prevented by previous bilateral adrenalectomy but that thymic atrophy will follow in these animals if they are given substitutive therapy with adrenal cortical extract He further found that estrone will exercise an effect similar to that of the adrenal cortical extract More recently Evans and his group[167] found that the adrenocorticotropic hormone of the anterior pituitary lobe will produce thymic atrophy but only in the animal with intact adrenals Recently we were able to induce shrinkage of a thymic mass associated with myasthenia gravis by the administration of adrenocorticotropin[90]

The results of these anatomic studies both clinically and experimentally definitely portray the existence of a situation in which an autonomous 'see saw' arrangement is operative between these two glands It would appear that this physiologic interplay function is entirely independent of any of the other endocrine glands including the hypophysis The physiologic significance of this relationship is entirely obscure at present The fact that it occurs with such precise regularity however would suggest that the delicate balance exercised by these glands upon each other must be of considerable importance particularly perhaps early in life

With the more recent advances in our knowledge of the biochemical functions of the adrenal cortex it became possible to subject the thymicoadrenal relationship to physiologic study The results are not entirely

satisfying or adequate but in a general way they are consistent with what had previously been observed anatomically. Thus Messini and Coppo[168] found that there was an increase in the blood chloride content of thymectomized rabbits. Marconi[169,170] found that this hyperchloremia was associated with an increased urinary chloride excretion, a rather paradoxical observation. In addition, he demonstrated that hypochloremia could be induced by the administration of thymic or lymph gland extracts. Finally, Parhon and Werner[171] showed that thymus extract caused a decrease in serum potassium.

With this experimental basis as a background, Segaloff and Nelson[172] studied the effect of thymectomy on the course of adrenal insufficiency in the bilaterally adrenalectomized rat. They found that thymectomy failed to influence either the survival period or the growth curve of these animals and concluded that "despite any effect the thymus may have upon the function of the adrenals, or upon the adrenal-controlled physiologic processes, it is quite inadequate to cope with the acute situation in the adrenalectomized animal."

The recent work of Dougherty and White[173] and of Simpson, Reinhardt and Evans[174] suggests that the adrenals play some part in determining the size of lymphoid tissue. In an interesting series of papers dealing with the adrenal cortical control of antibody release from lymphocytes, Dougherty and his coworkers[175] have apparently demonstrated that the control of the size of lymphoid tissue is dependent on the ability of the adrenal cortex and its extract to induce dissolution of lymphocytes. Following the administration of whole adrenal cortical extract there occurs an absolute lymphopenia in the circulating blood and as a result a reduction in the size of lymphoid tissue. According to these investigators this phenomenon appeared to be a function of the adrenal cortex specifically since it can be produced by other agents including adrenocorticotropic hormone of the anterior pituitary only in the presence of intact adrenals. The results of these studies are consistent with the observation so frequently noted in the autopsy on patients with Addison's disease who show a diffuse lymphoid hyperplasia.

Relation of the Adrenals to the Parathyroid Glands.—As early as 1908 Eppinger, Falta and Rudinger[176] suggested the existence of an antagonistic relationship between the adrenals and the parathyroids. They observed a decreased carbohydrate tolerance after parathyroidectomy and attributed it to an inhibitory effect of the parathyroids on the sympathetic nerves. This was in contrast to the exciting influence of adrenalin upon the same nerves. These conclusions received some support from the work of Falta and Kahn[177] and of Hoskins and Wheelan[178] who demonstrated that patients with tetany showed an increased response to adrenalin. Contradictory results, however, were obtained by Kylin[179] and by Crepa and Fernbach.[180]

With an increase in our knowledge of the physiology of the adrenal cortex attention was then focused on the relation of that part of the adrenal to the parathyroids. Schour and Rogoff[181] emphasized the possible existence of such a relationship by noting that the disturbances in the calcification of the dentin of rats incisors after adrenalectomy was similar to that seen

after the administration of parathormone. In addition, Rogoff and Stewart[152] found a considerable hypercalcemia in adrenalectomized dogs associated with marked parathyroid hypertrophy.[153] However, these results could not be corroborated by other investigators.[99, 184]

It is an interesting observation of Shelling[185] that the effects of acute parathormone overdosage are similar to those observed in acute adrenal insufficiency in regard to blood chlorides and sodium and water metabolism. Following the repeated administration of large doses of parathormone to the normal dog, there occurs a marked diuresis associated with a considerable urinary excretion of chlorides and sodium in addition to the calcium and phosphorus. This is associated with hemoconcentration, elevation of the blood urea and non-protein nitrogen, and a decrease of serum chlorides and sodium.[186] This is followed by anorexia, vomiting, diarrhea, and eventually vascular collapse and death.

On the basis of the meager experimental data available, it is difficult to feel that there is any particularly significant relationship between the adrenals and the parathyroid bodies. This view is essentially in agreement with those of Shelling[185] and Grollman.[11]

The Relation of the Adrenals to Shock.—Shock is characterized essentially by profound circulatory failure induced by a marked reduction in blood volume. As pointed out by Moon[187] in his excellent treatise, the circulatory collapse seen in shock is neither cardiac nor vasomotor in origin. The general mechanism involved in the development of the shock picture may be described as follows. The first pathologic phenomenon to occur is a reduction in blood volume due to loss of plasma. The hemoconcentration which thus results induces a reduction in cardiac output and increasing anoxemia. These factors precipitate circulatory collapse with eventual fall in blood pressure and failure of renal function.

In surgical shock as it is generally encountered, in the shock of burns, of extensive trauma, of histamine, adrenalin and allied substances, the loss of plasma is due primarily to increased capillary permeability, which permits of the leakage of the fluid through the capillary walls, and dilatation and stagnation in the capillary bed. It would appear superficially, then, that at least under these circumstances the shock phenomenon is entirely a mechanically induced one. It is perhaps not difficult to grasp that in instances of experimental and clinical trauma, in surgical procedures and in burns, the local injury thus engendered may be associated with extensive capillary damage. However, the fact that histamine, for example, is capable of inducing the classical picture of shock promptly raises the question concerning the role that various toxic agents may play in the production of this phenomenon. During the first world war, allied commissions set up to study the problem of shock observed that the application of a tourniquet to an injured extremity prevented the development of shock. The removal of the tourniquet, however, was promptly followed by the development of the shock picture. It was postulated, therefore, that following such traumatizing injury some metabolites, histamine-like in character, or perhaps some other protein decomposition products, were formed in the injured area and when liberated into the circulation induced increased

generalized capillary permeability, with consequent loss of plasma and the resultant picture of shock.[18]

This clinical observation subsequently received ample experimental confirmation and was referred to as the "toxic theory of shock." In subsequent analysis and repetition of these experiments, however, certain discrepancies became apparent. Thus Selye and Dosne[183] successfully repeated these experiments in monkeys and found that following release of the occlusion shock developed before any significant amount of edema was evident in the damaged area. However, they found in addition that blood taken from the intact extremity and injected into adrenalectomized mice was no less toxic than that obtained from the occluded extremity. They concluded that these observations were inconsistent with the toxic theory of shock.

Duncan and Blalock[189] approached the problem by placing the posterior extremity of an anesthetized animal into a mechanical press with uneven surfaces, thus producing a crush injury. During the period of actual crushing no shock manifestations were evident. Removal of the extremity from the press (in which it had been for five hours) was followed promptly by swelling of the thigh, hemoconcentration, decline in blood pressure, oliguria, *etc.* Of 19 animals subjected to this experiment only 1 survived. However, when immediately upon removal of the leg a pneumatic cuff exerting a pressure of 40 millimeters of mercury was applied, 15 of 21 animals survived. The authors felt that this result was due to a lessening of local fluid loss, and bore no relationship to the release of toxic metabolites since there was no evidence that the pneumatic tube caused venous obstruction. These experiments are not entirely conclusive, since it is impossible to know on the basis of their data whether toxic substances actually *did not find their way into the general circulation*. Finally, Heuer and Andrus[190] confirmed previous observations in which shock was produced following the injection into intact animals of aqueous extracts obtained from closed intestinal loop.

The problem was further elucidated by observations in medical conditions associated with shock, such as diabetic ketosis, cholera, intestinal obstruction, acute adrenal cortical insufficiency, etc. The patients with severe diabetic ketosis, cholera, and high intestinal obstruction present a clinical picture identical with that observed in the previously discussed conditions. They, too, show marked fluid loss, hemoconcentration, reduction in blood pressure, renal failure, and finally circulatory collapse. These phenomena in medical shock are more gradual in development, but the end result is a complete and typical clinical picture indistinguishable from true traumatic or burn shock.

In these medical states one need not postulate the existence of a toxic agent which induces fluid loss. The loss of fluid in high intestinal obstruction is due primarily to vomiting, while in cholera the severe diarrhea causes the dehydration. In diabetic ketosis both vomiting and excessive diuresis play a most important role in the development of dehydration and reduction in blood volume. In these conditions there also occurs an increase in capillary permeability, but this factor is not as important as it is in the shock of burns or trauma.

We may summarize then the status of shock essentially as follows This condition is due primarily to a loss of fluid This loss of fluid results in dehydration and hemoconcentration The reduction in blood volume in turn is associated with a fall in blood pressure, reduced cardiac ouptut eventual renal shutdown and finally circulatory failure The circulatory failure which thus ensues is essentially a peripheral phenomenon and not cardiac in origin *Increased capillary permeability with capillary dilatation* and stagnation probably occurs in all states of shock but not always is it the primary source of fluid depletion In certain conditions excessive vomiting diarrhea, urinary diuresis or severe diaphoresis represent the major portals through which fluid is lost Under certain circumstances too toxic agents such as histamine or other protein breakdown products play a primary role in producing marked capillary damage which predisposes to leakage of fluid It is not unlikely that in most cases of shock some toxic products are formed as a result of the capillary stagnation and anoxemia which play a further contributory although secondary part in the pathogenesis of this state

The chemical evidences of shock are reduction in the levels of the blood chlorides and sodium and according to some authors an increase in the total proteins of the serum essentially as a phenomenon of hemoconcentration, and an increase in the blood urea and non protein nitrogen creatine *and creatinine These last changes occur secondarily to the progressive* renal failure The pathologic changes in shock are characterized by distention of the capillary beds constriction of peripheral arterioles marked congestion of the abdominal viscera particularly the mucosa of the gastro-intestinal tract Frequently small superficial punched out ulcers are found in the stomach duodenum and upper part of the small intestine Marked congestion of the rectal mucosa is often observed The kidneys show pronounced tubular degeneration

As we review the picture of shock in general we realize that it bears a close similarity to that observed in acute adrenal insufficiency Indeed Addisonian crisis is characterized by dehydration hemoconcentration low blood pressure, renal failure and circulatory collapse The blood chemical findings are essentially those described above for shock in general In short the picture of Addisonian crisis is that of a patient in shock In view of the prompt response of these patients to specific hormone therapy it was inevitable that the question concerning the relationship of the adrenal cortex to shock be raised

The pathogenesis of adrenal crisis has been amply dilated upon elsewhere in this book (p 178) In addition there is considerable evidence to indicate that in adrenal cortical insufficiency there exists also a disturbance in capillary permeability This observation was noted as early as 1909 by Athanasis and Gradinesco[193] and has since been confirmed[30 191 195] In these respects, then the peripheral vascular collapse of adrenal insufficiency is identical *with that observed in other conditions*

The evidence in favor of a specific and fundamental relationship between the adrenals and shock is meager The similarities between shock in general and adrenal cortical insufficiency prompted the suggestion of the existence of some cause and *effect relationship between the two* The tenability

of this hypothesis was further enhanced by the observation that adrenalectomized animals even when maintained in an excellent state of health with the use of adrenal cortical extracts readily developed shock when they were subjected even to moderate stress or trauma[196,197] Another approach to the problem was provided by the work of Weil and Browne[198] who found considerable quantities of cortical hormone in the urine of patients after operation They interpreted this as a compensatory effort on the part of the adrenals to prevent and minimize the development of shock Finally Selye and his coworkers[199] found characteristic changes in the adrenals during shock and demonstrated the existence of increased adrenal cortical activity during the recovery phase These authors suggested that shock states are associated with a relatively acute adrenal cortical insufficiency, resulting from a sudden unfulfilled need on the part of the tissues for the secretion of the adrenal cortex Zwemer[200] and Wohl and his group[201] describe the presence of histologic changes in the adrenal cortex in conditions associated with shock

Since the state of shock is induced primarily by excessive loss of fluid no matter what the cause of this fluid loss may be it is a reasonable assumption that adrenal cortical extracts may perhaps exert a beneficial effect in this condition Whole adrenal cortical extract and desoxycorticosterone cause fluid retention and furthermore Menkin[202] Freed and Lindner[203] and Swingle and his group[204] have demonstrated that whole adrenal cortical extract and according to the last named authors desoxycorticosterone reduce capillary permeability in the intact rabbit and in the bilaterally adrenalectomized dog

Whole adrenal cortical extract as well as various steroid fractions of the gland has been used extensively in the treatment of both experimental and clinical shock There can be no question but that adrenal cortical extract and desoxycorticosterone are effective both as a prophylactic and as a therapeutic measure in the prevention and combatting of shock in the adrenalectomized animal and in the patient with Addison's disease The role of these hormones in the intact animal or patient is much less clearly defined The abundant literature which has accumulated on this point is both confusing and contradictory and at present no definite conclusion can be reached In part this may be due to the differences in criteria employed for determining the existence of shock Finally one gathers from the literature that not all the various adrenal cortical fractions employed are equally effective Selye and his group[199] for example found that whole adrenal cortical extract was very effective in the prevention of shock in the intact rat while desoxycorticosterone was entirely without effect These results were confirmed by Weil and his coworkers[205] working with rabbits Perla and his coworkers[206] found that both desoxycorticosterone acetate and whole adrenal cortical extract were equally effective in the prevention of histamine and surgical shock Finally Noble and Collip[207] reported that the resistance of the intact rat to shock induced by trauma could be increased by the administration of various adrenal cortical hormones In contrast to the results obtained by these investigators Swingle and his group[208] found that neither whole adrenal cortical extract nor desoxycorticosterone acetate proved beneficial in the treatment

of shock induced by trauma or venous occlusion in non adrenalectomized dogs. Similarly Ingle,[209] employing adrenal cortical extract, corticosterone, 17-hydroxy-11-dehydrocorticosterone and 11-desoxycorticosterone, failed to observe any prolongation of the survival period resulting from the use of any of these adrenal cortical fractions in shocked non adrenalectomized rats.

The results in patients have been equally confusing, with the added disadvantage that the conclusions arrived at are essentially "impressions" and not the results of carefully controlled experiments. Perhaps the best series is that reported by Koster and Kasman.[10] These observers treated 100 patients preoperatively with desoxycorticosterone acetate and saline while a similar group of 100 patients was prepared preoperatively with saline alone. The surgical procedures in both groups of patients were of approximately the same severity. The mortality rate of the treated group was 11 per cent while that of the untreated group was 9 per cent. The authors felt that there was no evidence to indicate that desoxycorticosterone either prevented or favorably influenced shock when it developed. Similarly Besser[11] in a somewhat smaller group of patients found that desoxycorticosterone was of little value in preventing postoperative shock. In a much smaller group of cases Keating, Rynearson and Power[1] arrived at essentially the same conclusions. Perla and his coworkers[16] were impressed with the favorable results obtained with desoxycorticosterone acetate. They prepared 12 patients who were very poor surgical risks preoperatively with desoxycorticosterone acetate and saline and found that shock developed in none of these patients. Most satisfactory result in the treatment and combating of shock due to all causes including burns occurs with the use of cortisone or adrenocorticotropic hormone.

The results obtained in shock incidental to extensive burns are perhaps more satisfactory. With the exception of the later results reported by Rhoads and his group[13] who found no beneficial effects accruing from the use of adrenal cortical extract, most investigators were impressed with the fact that whole adrenal cortical extract as well as desoxycorticosterone acetate favorably affected the outcome.[191, 14, 1, 16, 217, 18]

Finally, there is evidence to indicate that both adrenal cortical extract and desoxycorticosterone favorably influence the development of hemoconcentration that ordinarily accompanies ether anesthesia. Thus Ragan, Ferrebee and Fish[19] found that desoxycorticosterone acetate caused a reduction in the loss of plasma volume occurring in patients during ether anesthesia. McAllister and Thorn[20] demonstrated similar results with whole adrenal cortical extract in the dog.

The Alarm Reaction. —The adaptation reaction as described by Selye[21] consists essentially of three phases: (1) the stage of alarm, (2) the stage of resistance and (3) the stage of exhaustion. The stage of alarm or the so-called "alarm reaction" was further subdivided into two phases, that of "shock," and that of "counter shock." When an experimental animal is subjected to stress or trauma, the initial response is that of shock characterized chemically by a reduction in the serum chlorides and sodium, an increase in serum potassium, a decrease in the blood sugar level, an increase in the urinary excretion of potassium and a negative nitrogen balance.

Clinically the experimental animal presents hypotension a reduction in the body temperature the formation of superficial ulcerations of the stomach and small bowel and hemoconcentration This phase which is of very short duration is followed almost immediately by the period of counter shock if the stress is not severe enough to result in the death of the animal during the shock period The phase of counter shock consists of a return of the electrolytic pattern to normal the blood sugar rises the body temperature and the blood pressure return to the previous control levels and at this stage hypertrophy of the adrenal cortex is evident The next stage which is the stage of resistance is a more prolonged phase and is manifested by a maintenance at normal levels of all the phenomena described above Where the trauma is persistent the final stage or stage of exhaustion may set in Here the electrolytes blood sugar blood pressure again return to shock levels the adrenal cortices show hemorrhage and necrosis and death ensues

This then is the picture of the adaptative mechanism One can see in effect that what is being described is the picture of shock as observed after any severe traumatic episode such as burns surgical operations severe infections *etc* This clinical and biochemical picture of shock is well known and has been described many times previously by various investigators Selye made the important contribution of recognizing the fundamental relationship of the pituitary and adrenal glands to this phenomenon Finally he emphasized the significance of the adaptative mechanism in the application of this exaggerated phenomenon to the smaller everyday trauma and stresses of life

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Chapter 9

ADDISON'S DISEASE

PATHOLOGY. CLINICAL DESCRIPTION. DIFFERENTIAL DIAGNOSIS.
SUPRARENAL APOPLEXY (WATERHOUSE-FRIDERICHSEN SYNDROME)

Introduction.—The first comprehensive report of the clinical picture of this disease was provided by Addison in 1855,[12] although a fairly accurate clinical and pathologic account of a case was presented by Bright[13] almost twenty-five years earlier. This case was included in the ones reported by Addison. Bright, however, failed to appreciate the cause and effect relationship between the clinical observations and the pathologic findings. Addison reported the histories of 11 patients with autopsy findings. Five of these showed extensive destruction of the adrenals due to tuberculosis. One was an instance of atrophy which Addison attributed to some inflammatory process involving the adrenals, and 4 showed malignant metastasis to the adrenals. The first 6 cases—those due to tuberculosis and the one of atrophy—presented the classical picture, and the signs and symptoms described by Addison cannot be improved upon today. He observed and commented upon the marked and curious pigmentation, describing its shades as varying between deep amber and chestnut brown. He pointed out that it can occur in a generalized form or present a patchy appearance. He noted its predilection for the face, neck, superior extremities, penis, scrotum, flexures of the axillae, and around the navel. He described the appearance of small dark spots (jet black freckles) generally over the body, in the mouth, and on the lips, and beneath the peritoneum of the mesentery and omentum. He described also the patchy areas of leukoderma in which the skin appeared startingly white and quite different from normal integument. He called attention to the marked weakness, anorexia, nausea and vomiting, constipation, and emaciation manifested by these patients.

In contrast to this group of patients, the 4 instances of carcinomatous metastasis to the adrenals presented a dubious clinical picture. In none of these cases were both glands involved. The description of the clinical picture was entirely lacking or limited in all 4. In the light of our present knowledge it would seem very doubtful that any of this group were true instances of Addison's disease. Carcinomatous metastasis to the adrenals occurs, but rarely is the destructive process extensive enough to produce the characteristic picture. Rowntree and Snell,[3] in reporting on more than 100 cases of Addison's disease, found that carcinoma was not responsible in a single instance, and in 70 cases of carcinomatous metastasis to one or both adrenals the clinical picture was not typical of Addison's disease.

Addison placed great emphasis on the presence of severe anemia in his cases. Actually he thought of the disease primarily as one of a curious kind of anemia associated with or perhaps due to the disease of the supra-

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healing that follows the administration of this hormone requires it be used cautiously.

The most common causes of Addison's disease, then, are tuberculous destruction and atrophy of the glands. In his original paper Addison[1] reported 11 cases, 5 of which were due to tuberculosis. Guttman[7] reviewed 566 cases of Addison's disease with postmortem studies from the literature. Bilateral tuberculosis was the etiologic factor in 70 per cent. The next largest group was due to atrophy and occasional cases were the result of amyloidosis, neoplasm, vascular lesions and pyogenic infections. A relatively uncommon although important form of Addison's disease is that noted in children with congenital adrenal cortical hyperplasia. This type of adrenal insufficiency occurs more frequently in the male infant, but may be associated with female pseudohermaphroditism. If the male child with congenital adrenal hyperplasia and adrenal insufficiency survives, virilism is noted. The adrenal failure in this group is solely in electrolyte balance since the corticoid excretion in the urine is quite normal and may even be increased while urinary androgen excretion is also increased.[116]

Rowntree and Snell[3] reported 31 cases of Addison's disease with autopsy findings, of which 84 per cent were due to tuberculosis. Barker[9] found 25 out of 28 cases and Conybeare and Millis[9] 22 out of 29 cases due to this etiologic factor. The remaining cases were due to simple atrophy of the adrenal cortex. In 1934 Snell[10] commented on the fact that the incidence of atrophy as a cause of Addison's disease seemed to be increasing. Of 30 recent postmortem examinations, 17 were due to atrophy and 13 to tuberculosis. Wells and his group[11] are in agreement with this observation and suggest that the extensive use of the more recently introduced drugs may be responsible for the increase in adrenal cortical atrophy. More recently Duffin[1] reported 17 instances of Addison's disease with necropsy studies. Ten of these cases were due to tuberculosis of the adrenals and 7 (41 per cent) to atrophy. In our own group of 46 cases of Addison's disease, 21 of which came to autopsy, tuberculosis was the causative factor in 18 instances and atrophy in 3. Very recently Sorkin[11] reviewed our cases and those in the literature.

When the adrenals are the seat of a tuberculous process, the entire adrenal is usually destroyed. It may be instructive to quote from the excellent and detailed pathologic studies reported by Barker[9] and quoted by Rowntree and Snell[3] in their monograph on Addison's disease. "In the sections of all of the 26 suprarenal glands there were typical areas consisting of tubercles with endothelial cells, giant cells, fibroblasts and lymphocytes. Acid fast bacilli morphologically resembling bacilli of tuberculosis were found in these sections in 11 cases. The bacilli were found in areas of necrosis, especially near their margins and not in the typical tubercules, giant cells, or endothelial cells. . . . In considering the histologic appearance of sections from these glands, the tuberculosis was found to be bilateral in all the 26 cases. It involved and almost destroyed the entire gland. The type of lesion varied between two extremes: a very proliferative type with many tubercles, many fibroblasts and connective tissue cells and only small areas of necrosis, and a type in which the gland was a mass of necrosis surrounded by a fibrous capsule in which there were only

renal capsules We realize today that anemia is not a particularly prominent or characteristic feature of this illness

Addison's description of this disease of the suprarenal capsules takes its place in the classical description of disease in history Although the account is modest and reserved very little has been added through the years to the clinical observations that he noted and reported A wealth of information has been gathered since then concerning the physiology and the underlying physiologic pathology of the adrenals the laboratory diagnosis and the treatment of the disease yet Addison's description of the pigmentation the weakness the gastrointestinal symptoms the wasting the feeble pulse and the fatal outcome still remains the basic clinical keynote for the diagnosis of this unfortunate illness

From the time of Addison's observations until comparatively recently very little hope could be entertained for the lives of patients afflicted with this disease Within the past fifteen years however our increase in knowledge concerning the underlying chemical disturbances and the isolation of specific adrenal hormones have altered the outlook considerably

CAUSE AND PATHOLOGY OF ADDISON'S DISEASE

The essential pathologic change in Addison's disease is the bilateral destruction of the adrenals There are two major causes of this destructive process fibrocaseous tuberculosis of the adrenals and atrophy These two causes account for the vast majority of instances of Addison's disease

Little[4] described the development of massive hemorrhage into the adrenals occurring mostly in children under the age of one (Waterhouse-Friderichsen syndrome or purpura fulminans) These cases however are also seen in adults and Herrick[5] has described a large series in Army practice during war This entity occurs particularly in the course of meningococcus infections and is associated with a fulminating and rapidly fatal outcome It does not produce the clinical picture of Addison's disease such as we see in the instances of more gradual and prolonged destruction of the adrenals

Necrotic changes hemorrhages and edema may occur in the cortex of the adrenals during the course of acute infections such as diptheria measles scarlet fever smallpox typhoid *etc* [6] but the destructive process is usually not extensive enough to produce the typical clinical signs and symptoms of Addison's disease It is a matter of conjecture as to whether the profound asthenia sometimes encountered during convalescence from acute infections notably la grippe may not be due to some temporary adrenal cortical injury It may be wise at this point to caution against the use of adrenal cortical hormone in this condition The adrenal cortex has extensive regenerative ability which can be interfered with seriously by the administration of a potent extract with the possibility of the development of atrophy of the adrenal cortex Quite recently the use of adrenocorticotropin postoperatively has been suggested in certain selected cases found to have a relative adrenal insufficiency as evidenced by a high eosinophil count in the circulating blood [10] However the interference with wound

only one of the series in which there was no pigmentation Barker concludes that it would appear that the tuberculous process (in the suprarenals) is always progressive until the gland is almost completely destroyed

Small areas of healed tuberculosis such as is commonly seen in the lungs liver and spleen have not been found in the suprarenal glands

Tuberculosis of the adrenals is usually although not always associated with active tuberculosis elsewhere Of the 26 cases described by Barker 22 had morphologic evidence of active tuberculosis elsewhere in the body

Addison's disease due to atrophy of the adrenals presents a fairly typical pathologic picture well summarized by Guttman [7] Grossly the adrenals are extremely small and are found at necropsy only with the greatest difficulty

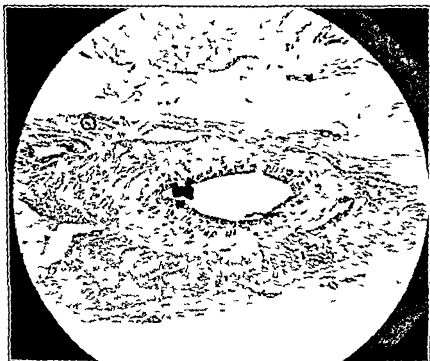


Fig 13 —Bilateral adrenal atrophy producing Addison's disease Note almost complete disappearance of adrenal cortex and prominence of central vein

Sometimes it is necessary to remove the blocks of tissue in the region of the adrenals and section it finely in order to identify remaining suprarenal tissue Microscopic examination shows either a complete loss of the cortex or such extensive destruction that only isolated remnants or small islands of regenerated cortical cells are seen According to Duff and Bernstein [13] the zona reticularis of the cortex disappears first while the zona glomerulosa persists longer As a result of the progressive necrosis of the adrenal cortical cells there is collapse of the stroma with an apparent increase in fibrous tissue There is usually also an increase in fibrous supporting framework in the medulla with some shrinkage in the medullary cells In addi

a few tubercles and a small number of lymphocytes. The necrosis consisted of a homogeneous mass, in which there were occasionally fine particles of calcium and often fat droplets near the margins. Grossly the necrosis differed from the ordinary caseous necrosis of tuberculosis in that the necrotic process was yellow or yellowish gray, firm and rubbery and on section presented a uniform surface. This gross picture is well known to pathologists as being characteristic of Addison's disease and differing from most tuberculous necrosis found in other parts of the body. As a rule the glands were found to be definitely enlarged. The largest pair weighed 27 and 28 grams respectively, compared with a normal weight of 4 to 10

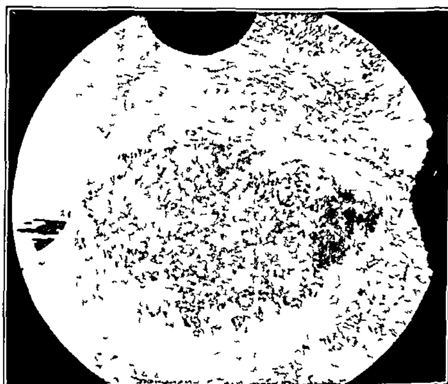


Fig. 12.—Photomicrographic section of the adrenal of a patient with Addison's disease due to bilateral adrenal tuberculosis.

grams. In only one case was there any gross calcification, and about half the substance was replaced by a hard stony mass of calcium salts. Whenever possible numerous sections of the gland were examined to determine whether any suprarenal tissue remained. Some cortical tissue was found in 24 of the 26 cases, seen as small islands of cortex near the periphery or as cortical adenomas near or beyond the margin of the tuberculous process. The amount of this suprarenal cortical tissue was estimated at less than 5 per cent of the normal amount. In only 1 case was any of the medulla of the suprarenal glands seen and in this case the amount was in a small area. This case, however, was the

only one of the cases in which there was no pigmentation. Barker concludes that "it would appear that the tuberculous process (in the suprarenals) is always progressive until the gland is almost completely destroyed. Small areas of healed tuberculosis such as is commonly seen in the lungs, liver and spleen have not been found in the suprarenal gland."

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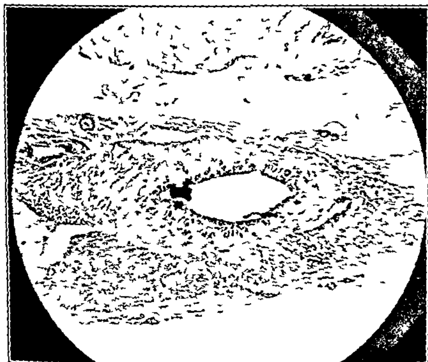


Fig. 12.—Bilateral adrenal atrophy producing Addison's disease. Note almost complete disappearance of adrenal cortex and prominence of central vein.

Sometimes it is necessary to remove the blocks of tissue in the region of the adrenals and section it finely in order to identify remaining suprarenal tissue. Microscopic examination shows either a complete loss of the cortex or such extensive destruction that only isolated remnants or small islands of regenerated cortical cells are seen. According to Duff and Bernstein[12] the zona reticularis of the cortex disappears first, while the zona glomerulosa persists longer. As a result of the progressive necrosis of the adrenal cortical cells there is collapse of the stroma with an apparent increase in fibrous tissue. There is usually also an increase in fibrous supporting framework in the medulla with some shrinkage in the medullary cells. In addi-

tion to the above findings there is also abundant infiltration of lymphocytes into the medulla and among the remnants of cortical cells. In general the process of atrophy mostly affects the cortex. The medulla is left fairly intact except for the minor changes described above while the cortex is usually entirely destroyed. Only relatively infrequently does the medulla seriously share in the extensive necrotizing destructive process.

The nature of this destructive atrophic process is by no means clearly understood. That it is nontuberculous in character is generally accepted. It would seem on the basis of the available data that the process is of a chronic inflammatory character probably due to some destructive agent with a selective affinity for the cells of the adrenal cortex. The nature and character of this destructive agent is of course a matter for speculation. The fact that signs of adrenal insufficiency so often follow upon the subsidence of acute systemic infections would suggest that bacterial toxins may play an important role in this destructive process. Well[14] compared the lesions in the adrenals with acute yellow atrophy of the liver and suggested that unknown toxins of a similar nature were responsible for both processes. At present we must be content with Brenner's[15] cryptical conclusions that it is a primary toxic atrophy or a low grade chronic inflammatory process of unknown etiology.

The term "atrophy" is actually a misnomer. There occurs no atrophy in the true sense of the word since a gradual shrinkage in the size of the individual cells does not take place. As far as can be determined there is no impairment in the circulation of the adrenals which results in the disappearance of the cortical cells.[13] The pathologic process is rather one of destruction of the adrenal cortical cells.

The effect of Addison's disease on the other organs, particularly the endocrine glands, is a matter of great interest. It is rather a surprising phenomenon how little pathologic alteration can be demonstrated in the other glands, especially in view of the functional endocrine changes which are manifested. Thus loss of libido, amenorrhea, lowered basal metabolic rate and disturbances in carbohydrate metabolism are so frequently seen in this disease.

At the autopsy the pathologic changes in the other endocrine glands, with the exception of the hypophysis, are comparatively slight. Crooke and Russell[16] report the microscopic findings in the pituitaries of 12 cases of Addison's disease, 5 of which were due to atrophy and 7 to tuberculosis of the adrenals. Serial sections and differential enumeration of the cells of the anterior hypophysis showed an increase in percentage of the chromophobe cells, a slight reduction in the number of acidophil cells and a very great reduction in the number of basophil cells. This last was a constant feature. In addition there was an increase in the number of basophil transitional cells, these frequently being more numerous than the ripe basophil cells. Kraus[17] reported somewhat similar findings several years previously in 4 cases of Addison's disease. Duffin[1] confirms these findings and describes a mild degenerative process involving the basophil cells. In 2 of our group of 18 patients with tuberculous destruction of the adrenals there was almost complete atrophy of the anterior lobe of the hypophysis. This is particularly interesting in that such anterior pituitary destruction

apparently occurred secondarily to primary disease of the adrenals. One might expect, as indeed one often finds, that atrophy of the anterior lobe of the hypophysis such as occurs in Simmonds' disease is associated with narrowing or atrophy of the adrenal cortex. The fact that the reverse can occur indicates the presence of a more delicately balanced and reciprocative relationship than is expressed by the oversimplified concept of the pituitary as the "master gland." The testes, ovaries, and pancreas are usually free of any pathologic changes, although in one case of adrenal cortical atrophy there was associated atrophy of the ovaries. The thyroid not infrequently shows some increase in fibrous tissue, a moderate lymphocytic infiltration, and occasionally signs of hyperactivity. Occasionally there is a persistent thymus, but this does not occur with any greater frequency than is seen in the general population. In instances of adrenal cortical atrophy, more so than in tuberculous destruction of the suprarenals, there is frequently noted a generalized lymphoid hyperplasia and a lymphocytic infiltration of most of the organs of the body.[12]

Summary of Pathologic Findings.—The most common causes of Addison's disease are tuberculosis of the adrenals and atrophy. The latter is not a true atrophy but a curious destructive process, the etiology of which is at present unknown. Tuberculosis of the adrenals accounts for from 60 to 90 per cent of the cases of Addison's disease, while atrophy is the cause of the remaining instances. Within recent years there has occurred an increase in the incidence of Addison's disease due to atrophy of the suprarenals. The tuberculous process, when present, involves the entire gland, both cortex and medulla being destroyed. In contrast, in atrophy of the adrenals the cortex is completely destroyed but the medulla is usually spared except for relatively minor changes, such as an increase in fibrous tissue and dense lymphocytic infiltration into the medullary parenchyma. Such lymphocytic infiltration into the medulla is by no means limited to the cases of atrophy, but is also seen in tuberculous destruction of the adrenals, although in the former the lymphocytic infiltration is more extensive and dense.

Tubercle bacilli, if carefully searched for both by section stain and smear, can frequently be demonstrated in the tuberculous adrenals. In Addison's disease due to tuberculosis there is usually, but by no means always, pathologic evidence of active tuberculosis elsewhere.

In Addison's disease, whether due to tuberculosis or atrophy, there is relatively little involvement of the other endocrine glands demonstrable pathologically, with the exception of the pituitary and thyroid glands. The testes and ovaries may show some atrophy, but are usually normal, although small in size, both grossly and anatomically. The pancreas generally shows no changes, while a persistent thymus is only infrequently seen. The pituitary changes have already been described. In adrenal tuberculosis and in most instances of atrophy the thyroid may show some lymphocytic infiltration and fibrous tissue increase. However, in 2 cases of Addison's disease due to tuberculosis in our series of cases, extensive atrophy of the anterior lobe of the hypophysis was observed at autopsy, and both instances of adrenal atrophy of our group showed remarkable changes in the thyroid in which there occurred a dense infiltration of the lobules

with lymphocytes and plasma cells and even replacement of the acini with these cells. In addition there was almost complete replacement of the thyroid tissue with connective tissue so that the gland looked like a mass of fibrous tissue infiltrated with lymphocytes and plasma cells.

At the Mount Sinai Hospital in New York City 48 instances of Addison's disease were seen since 1928. Of these, 21 were examined at necropsy. In 18 of these 21 cases the Addison's disease was due to tuberculosis of the adrenals and 3 were due to atrophy. It might be of interest to present briefly the autopsy findings of the pertinent organs in some of these cases.

Illustrative Cases

CASE 1.—This patient was a male aged fifty. The final anatomic diagnosis was caseous tuberculosis of both adrenals with complete destruction, fibrous pleural adhesions of the right side, old tuberculous scar of the apex of the left lung, and adenoma of the prostate.

Upon gross examination the heart was small and flabby; the right circumflex coronary artery showed a small amount of sclerosis while the aorta was elastic and presented few atheromatous changes. The thyroid was normal in size and the thymus consisted of fatty involutional tissue. The adrenals were very firm and cut sections of both glands showed extensive caseating areas. The medulla and cortex were not discernible. Associated with the right adrenal in the periadrenal tissue a small nodule about 3 × 3 millimeters was found. On microscopic section this proved to be accessory adrenal tissue.

On microscopic examination the heart showed extensive degenerative changes of the muscle fibers and nuclei and there were several small foci of lymphocytic infiltration. The thyroid appeared quite normal, the acini were filled with colloid and the lining cells were of moderate height. The thymus showed a fatty involution and there was no evidence of hyperplasia. Both adrenals *were completely caseated with only a narrow rim suggestive of adrenal cortical* tissue while the medulla was entirely destroyed. There was necrosis of the adjacent fatty tissue.

CASE 2.—This was a female aged fifty six. The final anatomic diagnosis was bilateral caseous tuberculosis of both adrenals, fibroid tuberculosis of the right upper lobe, primary infect of the left lower lobe, healed tuberculosis of the liver, acute purulent bronchitis, degeneration of the heart, liver, kidney, multiple uterine fibromata.

Upon gross examination bluckish brown pigment spots were seen on the *posterior peritoneal surface in the right peritoneal gutter. The heart was small* and the muscle flabby while the coronary vessels were widely patent. The aorta showed some moderate arteriosclerosis. Both adrenals were enlarged, particularly the left which was 5 times the normal size. The left adrenal had been converted into a sac the cavity of which contained cheesy and semifluid material. The appearance of the right adrenal was similar to that of the left and both were completely destroyed. The thyroid, pancreas and ovaries appeared grossly normal.

On microscopic study both adrenals showed a small number of isolated cortical cells. The caseous focus was completely encapsulated by dense fibrous tissue except in one small area *in which there was evidence of recent caseation*. There was a small amount of lymphocytic infiltration in and around the fibrous tissue. Tubercle bacilli were looked for but were not found.

There are several points to be noted in the autopsy findings of these cases of Addison's disease due to tuberculosis. It is of interest that calcification occurs so infrequently in the adrenals of these patients. The tuberculous process is a relentlessly destructive one where very little of the gland

escapes and in which the normal healing process with calcification rarely occurs Accessory adrenal cortical tissue was found in only one instance This is consistent with our clinical impression In routine autopsy material accessory adrenal cortical tissue is found very infrequently in humans in contrast to approximately 3 per cent in dogs

Tubercle bacilli were found in the adrenals in only one case in our series The probabilities are that tubercle bacilli could be found with considerably greater frequency if they are carefully looked for Both stained sections and smears must be utilized for this purpose

The comparative infrequency with which the other endocrine glands are involved is also noteworthy The thyroid shows some increase in fibrosis and lymphocytic infiltration and occasionally elevated acinar epithelium while the ovaries and testes are relatively unimpaired In two instances there was extensive atrophy of the anterior lobe of the hypophysis

Case of Adrenal Cortical Atrophy

CASE 3 —This patient was a female thirty-eight years of age The final anatomic diagnosis was Addison's disease due to primary atrophy of both adrenals fibrosis of both lobes of the thyroid with almost complete fibrotic atrophy of the upper half of the right lateral lobe huge calcified primary infect of the upper lobe of the right lung status five months after tonsillectomy

Upon gross examination the left adrenal was finally found and appeared as a shrunken nondescript structure It appeared to be composed of a number of firm cords running in a longitudinal direction with intervening softer collapsed areas On section the firm cords were seen as grayish solid masses in which no gross evidence of medullary or cortical tissue could be discerned Between the cords were cyst like spaces the walls of which were paper thin No right adrenal could be found Both lobes of the thyroid appeared shrunken in size On section the upper half of the right lobe seemed to be completely replaced by a dense mass of fibrous tissue while scattered throughout the remainder of both lobes were fine grayish white streaks of fibrous tissue

Upon microscopic examination several sections from the remaining adrenal tissue showed only fragments of medulla These consisted of small nests of atrophic cells densely infiltrated with lymphocytes and plasma cells and hyaline connective tissue No cortical cells could be identified The lobules of the thyroid showed a dense infiltration with lymphocytes and plasma cells which had invaded and in many areas replaced the acini Between the lobules as between the acini there was considerable connective tissue development and the upper half of the right lobe was completely replaced by this dense fibrous tissue The ovaries appeared atrophic

THE CLINICAL PICTURE

Incidence —Addison's disease is reputed to occur more commonly in men than in women In Thorn's series [6] of 158 cases there were 89 (56 per cent) males and 69 (44 per cent) females This is not quite so true in our group Of a total of 46 patients with Addison's disease 23 were males and an equal number were females The disease may afflict persons of any age but the greatest number of cases occur in the third and fourth decades The patients in our series ranged in age from eleven to sixty two years *See* Table 13 page 240

Addison's disease is of course a rare disease but with improvement in our diagnostic methods there has occurred a proportionate increase in its

incidence. In the twenty-year period in which the 46 patients in our series were observed, 1 case of Addison's disease was encountered among approximately 6,250 patients admitted to the various services of the hospital during the first half of this two-decade period. However, in the second half of this same period one case of Addison's disease was encountered among every 4,500 admissions.

TABLE 13.—AGE AND SEX DISTRIBUTION OF ADDISON'S DISEASE OBSERVED IN MOUNT SINAI GROUP

Age Group	*Number of Patients*	*Number of Males*	*Number of Females*
0–10	0	0	0
11–20	5	4	1
21–30	4	3	1
31–40	14	6	8
41–50	16	8	8
51–60	6	2	4
61–70	1	0	1
Total	46	23	23

Signs and Symptoms.—Addison described the disease as of slow and insidious onset so that "the patient can hardly fix a date to his earliest feeling of that languor which is so shortly to become extreme." In addition to the insidious onset, Addison emphasized the "general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change in colour of the skin." This classical description by Dr. Addison recorded almost a century ago can hardly be improved upon today. We have increased in our understanding of the underlying phenomena of the disease. Our methods of investigation and diagnosis have become elaborate and relatively certain, but we have added little to the dramatic clinical picture so concisely and vividly described by a great physician.

We think today of the disease as consisting of two major facets—the interim clinical picture during which the patient presents all the cardinal objective and subjective evidences of adrenal cortical destruction but continues to function fairly adequately, and the acute dramatic episodes of crisis. The signs and symptoms indicating the presence of this disease are present during both periods, and the episode of crisis really represents massive intensification of the clinical phenomena observed during the interim phase. The classical symptoms and signs are the profound asthenia, the gastrointestinal symptoms, particularly anorexia, nausea, vomiting, constipation or diarrhea, and occasionally relatively severe abdominal pains, marked weight loss, pigmentation and hypotension. The patient usually presents the story of a progressive asthenia. He notices a slow but continued loss of weight, develops a loss of appetite, and either becomes himself aware or is told by others of a change in the color of his skin.

In addition, the patients not infrequently manifest hypoglycemic episodes and curious mental changes characterized by marked irritability and per

PLATE I





Addison's disease with pigmentation of gums
Addison's disease with pigmentation in a scar on forearm

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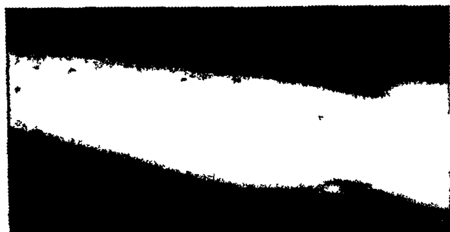
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PLATE II

Addison's disease with pigmentation in the creases of the fingers and palms

Addison's disease with pigmentation of fingers and knuckles. Note hand of a normal individual to the right

PLATE III





A Addison's disease showing dark freckling
B Addison's disease showing pigmentation of elbow (Right)

sonality alterations often severe enough to suggest an underlying psychosis of a persecutory character

The disease is usually insidious in onset but occasionally the first presenting evidence of the existence of the illness is the development of crisis precipitated by an acute infection or some surgical procedure Actually even in these instances a careful examination of the patient and a painstaking history will reveal the existence of previous evidences of the disease But in the complex civilization in which we live in which psychastheni is an almost universally accepted burden and sun tanning a universally employed therapeutic measure the finer nuances of the disease may be overlooked

Generally however the onset is slow The early symptoms may be asthenia and anorexia or the initial presenting symptoms may be pigmentation and hypotension The pigmentation and the low blood pressure may appear from several months to many years before any of the more disturbing symptoms occur In one instance in our series the patient developed well defined pigmentation and hypotension some eighteen years before gastrointestinal symptoms and weight loss appeared The onset of asthenia weight loss and gastrointestinal symptoms is always of ominous significance and indicates such extensive destruction of the adrenal cortex as to be life threatening It is interesting that this group of symptoms is of so much greater significance than the pigmentation and hypotension It has been suggested that the latter two are due primarily to involvement of the adrenal medulla That this is unlikely is evidenced by the fact that instances of Addison s disease due to atrophy of the adrenal cortex with slight or no involvement of the medulla manifest pigmentation and hypotension to a degree similar to that observed in tuberculous destruction of the adrenals We must conclude that both groups of symptoms are due to impairment of the adrenal cortex but that the anorexia and gastrointestinal symptoms will occur only after the greater part of the cortex is destroyed

Analysis of Signs and Symptoms —*Pigmentation* —The pigmentation of Addison s disease is due to the deposition of melanin in the skin and mucous membranes It represents a striking finding and occurs in a characteristic fashion in an extremely high percentage of cases Typical Addison s disease may occur in the absence of this finding Wilks[19] was the first to emphasize this possibility Lewin [3] reported on 684 cases collected from the literature and found that over 25 per cent had no pigmentation This data however is open to question since these cases represent reports of different observers with varying critical standards As a matter of fact there were 82 cases in this series in which the adrenals were found to be normal on pathologic study

More in keeping with our clinical impression is the report of Rowntree and Snell [3] who observed one instance of Addison s disease without pigmentation in a total of 108 cases More recently Lawson Beck and Murphy [4] reported another such proven case In our own group of 46 patients there was 1 proven instance in which the pigmentation consisted only of occasional black freckle and a few small patches of vitiligo of the upper margins of the forehead Thorn and his group [6] reported 158 cases all of whom showed the characteristic pigment deposits

from dioxyphenylalanine which may be a normal precursor of adrenalin. Because of adrenal disease the dioxyphenylalanine is not converted to adrenalin as promptly as usual and hence the dopa becomes fixed in the skin and is converted to melanin. More recently melanin pigmentation has been observed to occur in some patients following the use of either cortisone or adrenocorticotropin.

Whatever the cause of the pigmentation, its presence is an important objective evidence of Addison's disease, although it is by no means pathognomonic of the illness. As mentioned previously, the pigmentation may occur as an isolated clinical manifestation far in advance of the other characteristic changes of adrenal cortical deficiency. Six of our group of 46 patients had pigmentation for three or more years before other symptoms were evident. In 1 patient characteristic pigmentation was present for eighteen years before other symptoms indicative of adrenal cortical destruction developed. The remaining 5 patients were abnormally pigmented for four, five, six, seven, and ten years, respectively, prior to the appearance of the other symptoms. This interval during which pigmentation with or without hypotension is the only evidence of the disease may be a perfectly comfortable one for the patient and consistent with an active life. The patient in our group who noted a lapse of ten years between the time the pigment appeared and the development of asthenia was a dentist. During this ten year period he encountered no difficulties in performing the professional duties attendant upon a busy dental practice. It was only with the onset of asthenia promptly followed by gastrointestinal symptoms that his activities became seriously curtailed.

In general the degree and extent of the pigmentation bears no relationship to the severity of the Addison's disease, but the sudden intensification of the pigmentation in a patient with adrenal cortical deficiency may have ominous significance in that it may herald impending collapse. The relatively sudden increased darkening may be due to dehydration of the skin and underlying tissue and to an increase in cyanosis associated with Addisonian crisis and vascular collapse. With improvement following adequate therapy there occurs an apparent lightening of the skin color. This improvement in color is not due to an actual decrease of the pigment present in the skin but rather to improved hydration and circulation. The adrenal cortical hormones at present available for treatment exercise no direct effect on the pigmentation.

Arterial Hypotension. — The absence of hypotension, as of pigmentation, renders the diagnosis dubious. It is true that in patients with previous hypertension the subsequent development of Addison's disease may induce a fall in blood pressure to relatively normal levels. The disease, however, is characterized by a marked hypotension and this finding remains one of its outstanding features. The blood pressure of the Addisonian patient is subjected to the same fluctuations on exertion and excitement and to the same diurnal variations as are encountered in normal individuals.[8] Characteristically the systolic blood pressure is rarely over 110 and the diastolic above 70 millimeters of mercury. The usual range of systolic blood pressure is 80 to 100 millimeters of mercury and the diastolic below 70. In crisis the blood pressure is, of course, considerably lower and not infre

The diagnosis of Addison's disease in the absence of pigmentation is hazardous and should not be made unless the clinical impression is confirmed by the unequivocal demonstration of the characteristic laboratory disturbances. Unless this precaution is observed, many psychasthenic patients will be subjected to needless harrowing experiences, invalidism and expensive therapy.

The pigmentation has been described variously as tan, suntan, brown, smoky and negroid. All of these varieties were observed in our series. Not infrequently the pigmentation will begin ostensibly as a sun tan which, however, persists and becomes permanent and with the passage of time becomes progressively darker. Actually in most instances there is a qualitative difference between the pigmentation acquired after exposure to the sun and that of Addison's disease, but exposure to light may perhaps play some role in the production of this symptom since generally the ominous discoloration is first observed and the pigmentation is darkest on the skin of the exposed parts.

Of greater clinical significance, however, is the presence of pigment changes in unexposed parts of the body. First in importance and frequency in this category are the unshapely patches of brown, brown gray, gray black or blue gray pigmentation observed on the mucous membrane of the oral cavity, particularly on the lips, gums, tongue, and occasionally on the posterior pharyngeal wall. Oral pigmentation is observed in most instances of Addison's disease and was seen in 36 of the patients in our group. One patient of this group was advised to seek medical care by his dentist who noticed the abnormal oral pigment. It should be emphasized, however, that not all patients with oral pigmentation have Addison's disease. Argyria, for example, is a not uncommon cause of such pigmentation superficially indistinguishable from that of Addison's disease. Similarly certain racial groups will normally show oral and general pigmentation.

Other types of pigmentation of significance in unexposed parts of the body are the increase in intensity of areolar, perianal and genital pigmentation. Equally significant is the appearance of pigmentation in operative scars, at pressure points such as the elbows, hat band region, or at places in the body where a restraining or tight fitting garment has caused pressure. Pigmentation is frequently observed in the folds of the axillae, the palms of the hands, and in the knuckles of the fingers. In addition to the diffuse pigmentation many patients develop scattered jet black freckles. Infrequently pigmentation is obesrved in the nails. One such patient had mahogany colored longitudinal bands in several fingernails extending from the base to the cut edge.

Addison[1] called attention to the areas of vitiligo or leukoderma occurring in this disease. These decolored areas are usually observed as small patches on the back and trunk and are reported frequently in association with destruction of the adrenal cortex. In our group this characteristic was observed in 3 instances (less than 7 per cent).

The mechanism of the production of the pigmentation is entirely obscure. Brown-Sequard suggested that a precursor of adrenalin is transformed into melanin. Block[20, 1..] advanced the hypothesis that the pigmentation was due to the presence of a specific oxidase in the skin which formed melanin

only when the subject is approaching or actually is in crisis In such instances the increase in blood pressure following the use of salt is incidental to an increase in circulating fluid and relief of the shock state The patient with Addison s disease whose blood electrolytes are normal and who is not in crisis will show no elevation of the blood pressure following administration of salt The effect of desoxycorticosterone however is much more specific It is interesting that while whole adrenal cortical extract exercises relatively little effect on the blood pressure in the sense that it does not induce hypertensive levels desoxycorticosterone exercises very marked effects Whole extract will elevate considerably the blood pressure of the patient in crisis and it will cause some increase even during the interim state when the patient is relatively well but hypertension is never induced Desoxycorticosterone acetate however can induce hypertension in the normal individual as well as in the patient with Addison s disease The degree of the effect of this compound is dependent on the integrity of the adrenal cortex Thus while hypertension can be produced in the normal individual and in experimental animals with intact adrenals this hyper tensive effect is more readily elicited in the patient with Addison s disease or in the adrenalectomized animal These studies suggest that desoxycor ticosterone has a specific blood pressure raising effect Furthermore under normal circumstances the intact adrenal cortex produces blood pressure raising compounds such as desoxycorticosterone as well as cortical fractions which control and balance the effects of the former

Gastrointestinal Symptoms —Gastrointestinal symptoms in patients sus pected of having Addison s disease always indicate the presence of exten-sive adrenal cortical destruction Patients may continue for many years with pigmentation and hypotension and conduct their affairs adequately but the development of persistent or recurrent gastrointestinal symptoms heralds serious incapacitation and threat to life The initial gastrointesti nal symptom to manifest itself is usually anorexia Later the patients develop nausea vomiting and constipation Occasionally abdominal pain and diarrhea will be present The anorexia is usually insidious in onset becomes progressively more severe and may attain such profound propor tions that the mere sight of food induces nausea and vomiting Anorexia was observed in over 80 per cent of our patients Nausea and vomiting occurred almost as frequently while diarrhea was observed in only 5 of our 46 patients

Abdominal pain occurs in a relatively small percentage of the patients Usually this pain is of a vague and nondescript character Occasionally however it may be severe and simulate acute intra abdominal disease One patient in our group was suspected of having a peptic ulcer prior to admis sion to the hospital because of epigastric pain which occurred when he was hungry and which was relieved by the ingestion of food and alkaline powders X ray studies of the stomach and duodenum failed to reveal the presence of any organic lesion When the true nature of the illness was recognized and treatment with salt and cortical extract instituted the ab dominal pains promptly vanished It is noteworthy in the light of this case that when the gastrointestinal symptoms are severe the stomach is usually the seat of an angry gastritis Occasionally ulcerations have been

quently is unobtainable. The average systolic pressure obtained in our patients who were not in crisis and before treatment had been started was 90 millimeters of mercury, while the average diastolic pressure was 60. One patient who had had hypertension prior to the development of Addison's disease had a blood pressure of 140/70. During the course of the illness, however, the blood pressure became progressively lower and eventually reached hypotensive levels.

The hypotension observed in the patients with Addison's disease frequently has a postural component. The symptoms associated with a postural hypotension thus constitute a considerable part of the symptomatology. The dizziness, blurring of vision, sense of faintness, cardiac palpitation and tachycardia, and occasionally even angina are noted to occur particularly with change in posture and most frequently on arising in the morning. It is of interest that the postural hypotension remains unaffected by adequate therapy with salt and cortical extracts. In 1 patient in our series, giddiness and syncope were prominent initial symptoms. Hypoglycemia as an etiologic factor in the production of these symptoms was definitely excluded by suitable studies. Morning weakness and syncope with rapid pulse and drop in blood pressure continued to recur in *this patient following the rapid assumption of the vertical position* despite very adequate treatment with salt and desoxycorticosterone acetate. The salt and extract produced a definite increase in the basal level of the blood pressure but did not influence its postural fall.

The explanation for the postural hypotension encountered in these patients is obscure and is probably related to a decrease in vasomotor tonus. Rowntree and Snell[3] have emphasized that this lack of vasomotor tonus is not encountered in essential or relative hypotension, and that the drop in blood pressure in idiopathic postural hypotension is not ordinarily accompanied by an increase in pulse rate.

The cause of the hypotension in Addison's disease is also obscure, but there are several factors which unquestionably play significant roles. The fact that it occurs with equal frequency in instances of adrenal cortical atrophy with intact medulla and in tuberculous destruction of the entire adrenal would suggest that epinephrine has little to do with its pathogenesis.

An increase in the blood pressure to relatively normal levels has been observed following the use of salt and water alone, desoxycorticosterone or whole adrenal cortical extract without salt. Such improvement in the blood pressure in the adrenalectomized animal following a large dose of cortical extract has occurred before any change in blood electrolytes or blood volume is demonstrable.[65] In view of the blood pressure raising effect of salt, Loeb[55] questions whether the increase in pressure may not be due at least in part to a specific ion effect on the blood vessels. Swingle and his coworkers[58] suggest that the elevation of the blood pressure following the use of desoxycorticosterone acetate results from an increase in the arteriolar and capillary tone.

One may question any *specific blood pressure raising effect of salt*. It exercises no such effect in the normal individual, and in the patient with Addison's disease or in the adrenalectomized animal this effect is noted

age varies between 20 and 30 pounds In our group one patient lost 65 pounds during the course of a year and another 60 pounds during a six-month period The smallest loss observed was 10 pounds and the average was 25 pounds

The loss in weight in this disease is apparent on inspection but although the patient shows considerable wasting he does not appear cachectic unless there is an associated progressively active tuberculosis This weight loss without the appearance of the cachexia observed in malignancy is a feature originally commented upon by Addison and subsequently reaffirmed by others The loss of weight is not only that of loss of body tissue but loss of body fluid as well, and not infrequently particularly if the patient is observed for the first time in crisis he appears 'dried out

The loss of weight is due primarily to four factors (a) The progressive anorexia and gastrointestinal disturbances (b) the insidious dehydration (c) actual wasting of muscles as evidenced by a disturbance in the creatine and creatinine metabolism and (d) changes in the other endocrine glands In association with the last category are such alterations as atrophic changes in the thyroid and anterior lobe of the pituitary which may condition weight loss

The weight curve as the other gastrointestinal symptoms can serve as a rough guide to the state of well being of the patient A progressive loss of weight indicates approaching adrenal insufficiency With adequate therapy there occurs an increase in weight due not only to improvement in appetite and increased food intake but also to restoration of body fluids A too sudden and marked weight gain following treatment with salt and cortical extract particularly desoxycorticosterone acetate indicates excessive fluid intake

Asthenia — The weakness of Addison s disease is of a profound character and its intensity an index of the degree of adrenal cortical insufficiency All patients manifest this symptom and in two-thirds of our group it was the first symptom to make its appearance The asthenia of the untreated patient is so marked as to constitute both a subjective and an objective manifestation The patient both looks and acts unutterably wearied even when lying in bed He may be completely incapable of any effort and no amount of rest in itself produces any improvement in this symptom The asthenia involves the entire organism Not only is there marked voluntary muscle weakness but the heart s action is extremely feeble the sounds distant and muffled and the radial pulses small and thready Blurring of vision dizzy spells and syncope in association with the hypotension and perhaps disturbances in carbohydrate metabolism are incorporated as part of the patient s feeling of marked tiredness and weakness The speech is often languid occasionally thick and slurred and calls for an effort that the patient is frequently incapable of making

There are several underlying factors which play significant roles in the pathogenesis of this symptom The prompt disappearance of the asthenia which occasionally follows the administration of intravenous salt and fluids alone and the frequent disappearance of this symptom with the use of cortical extract suggest that at least in good part the weakness must be related to the disturbed electrolyte pattern with its associated dehydration

noted in the stomach, duodenum, and first part of the jejunum. These ulcers are small, punched out, smooth-edged and superficial, rarely involving more than the mucosa. Rowntree and Snell[3] describe the occurrence of frank hemorrhage in some of their patients. The ulcerations are frequently multiple and are identical with those observed in bilaterally adrenalectomized dogs when the latter are permitted to develop acute adrenal insufficiency. These ulcers do not perforate and apparently heal promptly and completely when the patient recovers from the crisis.

The appetite of the patient with Addison's disease is capricious. A small percentage will manifest a definite salt craving. Thorn and his group[6] found this symptom to be present in 16 per cent of 68 patients. We found this to be true in an equal percentage of our group (15 per cent).

It should be borne in mind that patients suffering from Addison's disease may have abdominal pain due to unrelated pathologic conditions of the abdominal viscera. Thus, two of the patients in our series had biliary colic due to gallstones, and a third had an attack of acute appendicitis.

Patients with Addison's disease usually show a reduction in the gastric concentration of free hydrochloric acid, and actual achlorhydria has been observed frequently.[4] Such achlorhydria was noted in 50 per cent of our patients upon whom gastric analyses were performed. The degree of hypochlorhydria is dependent on the clinical status of the patient, and in this sense is an *essentially reversible phenomenon*. As acute adrenal insufficiency develops and the blood and tissue sodium and chlorides are depleted, the concentration of free hydrochloric acid in the stomach tends to drop. Following adequate treatment with salt and cortical extracts, when the body fluids are restored and the blood electrolyte pattern returns to normal, the hydrochloric acid in the gastric secretion reappears. This suggests that the achlorhydria is due to a diminution in the chloride ion available to the hydrochloric acid secreting cells of the gastric mucosa.

The achlorhydria apparently plays very little part in the production of the gastrointestinal symptoms. Approximately the same symptoms were presented by the patients whose gastric juice contained free hydrochloric acid as by those in whose gastric secretions none was found. The administration of dilute hydrochloric acid to Addisonian patients with achlorhydria failed to affect their abdominal symptoms. The anorexia, nausea, and diarrhea remained completely uninfluenced by this therapy.

The presence of the gastrointestinal symptoms always indicates impending crisis and calls for vigorous therapy. The intensity of these symptoms may serve as a rough index of the adequacy of treatment. Occasionally the onset of vomiting and diarrhea from other causes will precipitate acute adrenal insufficiency. This is, of course, related to the extensive loss of fluid and electrolytes which occurs as a result of the vomiting and diarrhea. Thus these symptoms may precipitate crisis, and also approaching crisis will produce and intensify *the gastrointestinal manifestations*. With adrenal insufficiency, if untreated, the nausea and vomiting may become intractable, but with treatment with intravenous fluids, salt, and cortical extracts they will be controlled.

Weight Loss.—Loss of body weight is a common and characteristic finding in Addison's disease. The weight loss is usually extensive and the aver

It is imperative to recognize the impending development of crisis and it is worth reemphasizing that the premonitory symptoms are an intensification of the usual symptoms of the disease

The factors which predispose to the development of this acute picture have become better defined with the increase in our understanding of the underlying physiologic pathology and treatment of adrenal cortical destruction We know now that unwise cessation of therapy with salt or extract or both will eventually result in crisis The presence of an acute infection however mild is a source of great danger unless compensated for by an increase in therapy Such infections are a veritable nemesis to the untreated patients while they constitute a much lesser danger to the treated ones Operative procedures of a most minor character may precipitate this unfortunate episode in the untreated patient Today with the impressive advances in therapy, the well treated patient will withstand the relatively minor procedures but major surgical intervention is still poorly tolerated This is particularly true of intraperitoneal procedures Undue effort and the injudicious administration of certain drugs notably thyroid extract, may help produce a state of crisis Collapse occurs particularly during the hot summer months when a good deal of salt is lost through increased diaphoresis

The mechanism of the production of Addisonian crisis has been discussed in detail in the chapter on physiology (p 178) However certain points are worth recapitulating briefly Although there are marked similarities clinically and experimentally between the crisis of Addison s disease and traumatic or secondary shock there are distinctive differences between the two and indeed the former has certain innate peculiarities of its own In both condition however the major external phenomenon is vasomotor collapse associated with a reduction in circulating blood volume increasesd concentration and viscosity of the blood elevation of the blood non protein nitrogen content and fall in blood pressure

The sequence of events that occurs in the crisis of Addison s disease and in the bilaterally adrenalectomized animals have been emphasized by Loeb [8] and by Harrop and his group [9,10] and may be essentially described as follows The initial and primary change that occurs is a loss of sodium and chlorides in the urine As emphasized elsewhere in this book the sodium ion is an intercellular ion intimately concerned with water metabolism and present in the intercellular fluid in isotonic concentration The excretion of sodium in the urine carries with it definite quantities of water and the excessive urinary loss of this ion in adrenal cortical insufficiency is associated with a proportionate loss of fluid The fluid thus lost comes from the intercellular tissue spaces This will be reflected in a corresponding decrease in the plasma volume since the latter serves as a compensatory reservoir which attempts to maintain the integrity of the extracellular fluid volume The loss of water from the tissue spaces is further increased by two additional factors In an attempt to maintain a normal osmotic relationship between the extracellular and intracellular fluid, water migrates from the tissue spaces into the cell since under ordinary circumstances the intracellular ions are incapable of passing the cellular barriers into the intercellular spaces This then represents another source of fluid loss

Salt and fluids by themselves, however, do not restore the muscular strength of the patient to the extent that cortical extract does. This was borne out by the experimental work of Ingle[57] who showed that while the work performance of the adrenalectomized rat was somewhat improved by the administration of salt, it was considerably improved by injections of whole cortical extract. Equally significant was the demonstration by this author[58] of the fact that the administration of desoxycorticosterone was less effective in increasing the work capacity of the adrenalectomized rat than was whole adrenal cortical extract or the carbohydrate active fraction corticosterone.

These observations would suggest that the asthenia of adrenal insufficiency is related not only to the disturbance in electrolyte metabolism but also to the underlying disturbances in protein and carbohydrate metabolism. It is possible, too, that whole adrenal cortical hormone has in addition a somewhat specific effect on the asthenia unrelated to either of the two factors described above.

From a clinical point of view, however, the strength of most patients will improve considerably when the distortion in the electrolyte pattern is corrected either by the use of salt and whole extract or of salt in conjunction with desoxycorticosterone. Although most patients show some disturbance in carbohydrate metabolism, only infrequently does it play a demonstrably significant clinical role in the asthenia. The additional use of cortisone increases the sense of well being and strength more than is obtained with desoxycorticosterone alone.

The Crisis of Addison's Disease.—The major life threatening hazard to the patient with Addison's disease is the development of crisis. This dramatic episode presents the picture of dehydration and shock and if not treated promptly and adequately will terminate fatally. Addisonian crisis occurs quite frequently, particularly in untreated cases. Not infrequently it serves to call attention to the previously unrecognized existence of the disease. In our patients it occurred at least once in 44 of the 46 patients.

The development of crisis is preceded by a few days, sometimes by a few hours, rarely by several weeks, by an intensification of the previously existing symptoms and by the addition of more severe gastrointestinal manifestations. There occurs a marked increase in weakness, the blood pressure falls, anorexia becomes profound, the skin color assumes a darker hue with a superimposed dusky slaty cyanosis. Nausea, vomiting and diarrhea become severe and sometimes intractable. Abdominal pain may develop, which may sometimes be severe enough to raise the suspicion of the presence of acute intra abdominal disease. These symptoms progress until the patients develop circulatory collapse. The blood pressure becomes unobtainable, the pulse thready and feeble, and the heart sounds distant and muffled. The skin is markedly dehydrated and the eyeballs are often soft and sunken into the orbits. The body temperature is usually lowered and the asthenia becomes so marked that slight effort on the part of the patient is fraught with the danger of a fatal outcome. Patients with Addisonian crisis rarely lose consciousness except as a preterminal event.

It is imperative to recognize the impending development of crisis and it is worth reemphasizing that the premonitory symptoms are an intensification of the usual symptoms of the disease

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from the tissue spaces, with a further compensatory decrease in plasma volume. Finally, nausea, vomiting and diarrhea contribute to the fluid depletion, although this phenomenon is evident only after adrenal insufficiency has become well established. Another indirect factor contributing to the fluid loss is the reduction in absorption of sodium and chloride ions from the intestinal tract, which occurs in the absence of intact adrenals.

With the progressive loss of intercellular fluid and reduction in circulating blood volume, marked dehydration and vasomotor collapse ensue and all the attendant phenomena such as hemoconcentration, renal shutdown, extrarenal azotemia and fall in blood pressure become evident.

*This is the common picture of Addisonian crisis but occasionally vaso*motor collapse and death will occur in the presence of perfectly normal blood electrolytes. Thus 3 of the patients in our series died of vasomotor collapse despite normal levels of blood sugar and electrolytes. These patients were admitted to the hospital in adrenal insufficiency with a normal blood electrolyte pattern and adequate blood sugar levels. Treatment with large quantities of adrenal cortical extract, desoxycorticosterone and intravenous glucose and saline as well as epinephrine failed to prevent a fatal outcome. In 1 of these 3 patients the vasomotor collapse and death occurred suddenly, while in the remaining 2 patients the downhill course was relatively slow and extended over a period of several days.

The manner of death in these patients is not dissimilar to that occasionally observed following shortly upon bilateral adrenalectomy in the experimental animal. The circulatory collapse in these instances must be due to adrenal cortical factors as yet unidentified but not related to electrolyte and water metabolism.

LABORATORY FINDINGS IN ADDISON'S DISEASE

The cardinal laboratory findings in this disease thus become clear. There is a decrease in the serum sodium and chlorides and elevation of serum potassium, blood urea and non protein nitrogen. There is an increase in the concentration of the blood as evidenced by a decrease in the plasma volume, increase in packed red blood cells and increase in the serum concentration of the total proteins. During crisis patients will frequently manifest varying degrees of acidosis. This at least in part is due to the fact that the urinary loss of sodium is considerably greater than that of chlorides.

Additional Laboratory Aids in the Diagnosis of Addison's Disease.—The laboratory picture just described is most characteristically observed in the patient in crisis. Here the decrease in blood sodium and chlorides and the elevation of potassium and increase in hematocrit and total serum proteins is marked and unequivocal. In periods between crises when the untreated patient is in a state of comparative well being the laboratory findings are by *no means so striking*. There may be slight although definite alterations in the electrolyte pattern but occasionally the deviations from the normal are so meager as to render the diagnosis on this basis alone doubtful. In these instances provocative measures may be employed which will bring out and emphasize the underlying electrolyte disturbances.

Salt Deprivation Tests — In 1933 Harrop, Weinstein, Soffer and Trescher[9] reported on the use of the salt deprivation test as an aid in the diagnosis of equivocal cases of Addison's disease. The patients were given a salt free diet, that is one containing less than 0.7 gram of sodium daily. Control samples of blood were analysed for sodium, chlorides, potassium, urea nitrogen and hematocrit. A twenty four hour control urine specimen was obtained and its sodium content determined. The patients were kept on this diet for forty-eight to ninety six hours and the above studies were repeated daily. On such a diet the patient with Addison's disease behaved in a characteristic fashion. There occurred an increase in the excretion of urinary sodium in excess of the intake, a progressive and definite fall in blood sodium and chlorides, and increase in urea nitrogen and blood potassium, and an increase in the hematocrit. This definite sequence of events was observed to occur only in Addison's disease. Normal individuals and patients with other illnesses could be kept for prolonged periods of time on a salt free diet without manifesting any of the typical changes seen in the patients with destructive lesions of the adrenal cortex. Actually it is not necessary to do the multitude of determinations outlined above as a provocative test. The demonstration of an increase in the excretion of urinary sodium above the intake or a definite fall in the level of the blood sodium renders the diagnosis of Addison's disease conclusive.

The test, however, is not without hazard since the patient with Addison's disease may be precipitated into a state of crisis upon the prolonged withdrawal of salt. The test therefore should only be performed in the hospital. The patient must be carefully observed and an adequate amount of potent cortical extract and intravenous salt must be immediately available for use if indicated.

In 1938 Cutler, Power and Wilder[21,3] modified this test for diagnostic purposes. The patients were given a diet with a standard amount of sodium chloride and potassium. In addition potassium citrate and water were administered in proportion to the body weight. The test is terminated after a fifty two hour period and the urine voided during the last four hour period is analysed for its concentration of chlorides. Under these circumstances patients with adrenal cortical insufficiency excrete urine with a high concentration of chlorides.

This test differs from the original salt deprivation test only in that the concentration of chlorides rather than that of sodium is determined in the urine. The patients are, of course, subjected to the same hazards and it must again be stressed that these tests should be undertaken only with a full awareness of the risks involved and the presence of adequate amounts of cortical extract and salt solution for immediate use if necessary.

Robinson, Power and Kepler[23] developed two closely related diagnostic procedures which show considerable promise. The first of these is based on the fact that patients with Addison's disease do not develop a prompt normal diuresis after the ingestion of large amounts of water. The two tests are conducted as follows:

The day before the test the patient is maintained on a regular diet from which extra salt is omitted. After the evening meal at 6 P.M. no further food or drink is permitted except that indicated as part of the test. At

10 30 P M the patient is asked to void and the urine is discarded All urine voided from this point until 7 30 the following morning is collected, measured and saved for chemical analysis At 8 30 A M the patient again voids and the urine discarded He is then given 20 cc of water per kilogram of body weight over a forty five minute period He again voids at 9 30 10 30 11 30 A M, and at 12 30 P M Each specimen is collected and measured At 11 30 A M blood is withdrawn under oil for chemical analysis

If the volume of any single hourly specimen voided during the morning is greater than the total volume of urine voided during the night, such a response indicates the absence of Addison's disease If on the other hand the volume of the largest hourly morning specimen is less than that of the night urine Addison's disease may or may not be present and the second half of the procedure is then performed as follows The plasma collected above is analysed for urea and chloride, and similar determinations are *performed on the noctural urine specimen The following formula is then* used to compute the result—

$$A = \frac{\text{Urea in urine (mgm \%)}}{\text{Urea in plasma (mgm \%)}} \times \frac{\text{Chlorides in plasma (mgm \%)}}{\text{Chlorides in urine (mgm \%)}}$$

$$\times \frac{\text{Volume of day urine (largest hourly specimen cc)}}{\text{Volume of night urine (total cc)}}$$

If the value for A in this equation is greater than 30 the patient probably does not have Addison's disease If the value for A is less than 25 the patient probably has Addison's disease provided that nephritis has been excluded

Two further procedures dependent on typical electrolytic response have been developed by Thorn and his group[34] and by Zwemer and Truszkowski[35] The first of these depends on the response of patients to the administration of a potent adrenal cortical extract To be of value this procedure must be conducted under carefully controlled conditions in which elaborate chemical determinations are necessary To rely on subjective improvement alone following specific therapy is entirely inadequate Zwemer and Truszkowski[35] have suggested the determination of the tolerance of patients to the ingestion of potassium as a diagnostic aid in adrenal cortical insufficiency Recent reports however have cast some doubt on the reliability of this procedure[36]

The Pituitary Adrenocorticotropic Hormone Test for Adrenal Cortical Insufficiency — This test was recently described by Thorn[11] It is based on the observation that following the injection of pituitary adrenocorticotropic factor in normal individuals there is an immediate fall in the circulating eosinophils and a rise in the uric acid excretion The procedure is as follows

No food is permitted after 8 P M On the following day 200 cc of water is given at 6 A M 8 A M and 10 A M The urine is collected from 6 A M to 8 A M, and an eosinophil count is done on the blood at 8 A M Immed

rately thereafter 25 mgm of adrenocorticotropic factor is injected intramuscularly The urine is then collected from 9 A M to 12 noon and an eosinophil count is again done at 12 noon The two urine specimens are analyzed for uric acid and creatinine and the uric acid—creatinine ratio is computed and the per cent decrease of circulating eosinophils is determined

The adrenocorticotropic factor is available in powder form the solubility of which varies with different batches The hormone is generally soluble in normal saline but sometimes requires alkalinization to a pH between 8 and 9 To 5 cc of sterile saline are added 3 drops of N/10 NaOH This is taken up in a syringe and added to the rubber-capped vial containing the adrenocorticotropic factor The vial is shaken gently and a somewhat cloudy solution is obtained This solution should not be kept longer than twelve hours at 4° C or for longer than two hours at room temperature

Thorn recommends the following technic for direct eosinophil counts The special diluting fluid used consists of

1% aqueous eosin	5 cc
Acetone	5 cc
Distilled H_2O to	100 cc

The diluent is filtered before use Oxalated blood is drawn into a white count pipette up to the 1 mark and the special diluting fluid is then used in the usual fashion The pipette is shaken and the counting chamber is filled immediately The eosinophils which stand out as red dots are counted after three minutes The average of 4 chambers is computed

Interpretation —Patients with Addison's disease show little or no drop in the eosinophil count while in normal subjects there occurs a 70 per cent or more reduction in eosinophils A 50 per cent reduction is considered the lower limit of normal This test is the simplest and the most useful for the determination of the adequacy of adrenal cortical function

In normal individuals following the injection of adrenocorticotropic factor there occurs an approximately 100 per cent increase in the uric acid—creatinine ratio Patients with Addison's disease show approximately a 20 per cent increase An increase of over 50 per cent is evidence against adrenal insufficiency

Carbohydrate Metabolism in Addison's Disease —In the clinical handling of patients with Addison's disease there are two major hazards that one must be cognizant of—the development of crisis and the development of hypoglycemic episodes Unlike the disturbances in electrolyte metabolism which occur in almost all patients with Addison's disease clinical disturbances in carbohydrate metabolism are by no means universal in these patients Thorn and his group [8] however observed some degree of abnormality of carbohydrate metabolism in 75 per cent of 52 patients Fifty per cent of this *group had episodes of spontaneous hypoglycemia* The degree of impairment of carbohydrate metabolism and the symptoms attendant upon this disturbance vary in different patients In some instances severe hypoglycemic episodes manifest themselves frequently and constitute a mortal danger to the patients while in other cases the disease

may run its entire course without the development of any hypoglycemic symptoms

However although the presence of symptoms dependent on carbohydrate disturbances may or may not occur underlying physiologic impairment of carbohydrate metabolism is demonstrable in most patients with Addison's disease This is the case also as originally demonstrated by Britton and Silvette[37] in the experimentally adrenalectomized animal

Porges[38] was perhaps the first to point out the frequency with which hypoglycemic episodes occurred in patients with Addison's disease and the fact that a similar phenomenon occurred in adrenalectomized dogs Later Maranon[39] demonstrated the marked sensitivity of these patients to minute amounts of insulin Levy-Simpson[40] carried this one step further and showed that patients with Addison's disease failed to show a rise in blood sugar comparable to that of normal individuals following the injection of a standard dose of epinephrine The fasting blood sugar levels of untreated patients with Addison's disease tend usually to be on the low side Thorn and his group[41] in 20 untreated patients found the fasting blood sugar level in most instances to be in the low normal range (80 milligrams per cent) The oral glucose tolerance curve in patients with adrenal cortical insufficiency usually yields a typical pattern characterized by a fairly low or low normal fasting blood sugar level a flat type of curve and a considerable degree of hypoglycemia several hours after the ingestion of glucose The intravenous glucose tolerance test on the other hand as used by Thorn and his coworkers[41] produces a normal height curve but with severe hypoglycemic reaction several hours later from which spontaneous recovery is difficult In several of their patients acute coma and vasomotor collapse was thus induced This difference in behavior between the oral and the intravenous glucose tolerance test would suggest that the flat curve in the former is due to poor intestinal absorption of glucose The administration of a potent adrenal cortical extract produced an increase in the fasting blood sugar level and prevented the development of the signs and symptoms of hypoglycemia Similar changes had been previously observed in adrenalectomized dogs by Kendall and his group[4]

Thorn[41] further found that the respiratory quotient of patients with Addison's disease who had a demonstrable carbohydrate defect was definitely elevated It is probable too that destruction of the adrenal glands in humans is associated with a disturbance in the intermediary metabolism of carbohydrates That this is true of the experimentally adrenalectomized animal is indicated by the fact that they have a diminished ability to convert lactic acid pyruvic acid and the amino acid alanine into dextrose[43] Thorn[41] found that injection of racemic sodium lactate failed to relieve the hypoglycemic symptoms of a patient with Addison's disease

These defects in carbohydrate metabolism observed particularly in the experimental animal are defects specifically related to disturbance in adrenal cortical function Thus Long Katzin and Fry[44] conclude that the administration of adrenal cortical extract decreases the proportion of glucose oxidized while increasing the proportion deposited as liver glycogen One of the properties of cortical hormone they hold is probably that of the stimulation of protein catabolism and conversion into glucose producing

an increase in the carbohydrate level and an increase in the nitrogen and potassium excretion The fact that whole adrenal cortical extract and to an even greater extent the specific adrenal cortical hormone 17 hydroxy 11-dehydrocorticosterone (cortisone) exercise such a profound effect on carbohydrate metabolism as to raise the fasting blood sugar level prevent the hypoglycemic episodes following insulin injections and the ingestion of glucose strongly emphasizes the specificity of this defect

It may be worth while to recapitulate the nature of the clinical disturbance in carbohydrate metabolism in patients with Addison's disease *Striking clinical abnormalities of carbohydrate metabolism are not frequently* observed in these patients Hypoglycemic episodes of varying severity however do occur and these episodes may terminate fatally One of the unfortunate aspects of the hypoglycemia in Addison's disease is that recovery does not tend to occur spontaneously The presence of hypoglycemia calls for prompt and vigorous therapy

Hypoglycemic episodes are frequently precipitated by fasting and by acute infections Since the patient with a carbohydrate defect is capable of utilizing essentially only readily available carbohydrates from an exogenous source the deprivation of food rapidly depletes the available carbohydrate stores and results in a further lowering of the already reduced blood sugar level Similarly the increased demand for carbohydrates such as occurs in the presence of acute infections and fever must be met with a greater carbohydrate intake

The patient with Addison's disease is unusually sensitive to insulin and even minute doses may precipitate him into severe hypoglycemic shock The use of this method then as a diagnostic aid should be avoided both because of the hazard involved and the paucity of information elicited The intravenous administration of glucose may produce a secondary hypoglycemic response It is wiser therefore to administer glucose in dilute solution and over a prolonged period of time

The evidences of disturbances in carbohydrate metabolism such as a low fasting blood sugar the flat oral glucose tolerance curve the tendency to hypoglycemic reactions the increased sensitivity to insulin and diminished response to epinephrine are not specifically diagnostic of Addison's disease but when present lend weight to the diagnosis

It is worth repeating that these disturbances when present are entirely independent of the status of the blood electrolytes

Relation of Addison's Disease to Diabetes Mellitus —Some disturbances in carbohydrate metabolism as evidenced by the level of the fasting blood sugar oral glucose tolerance and insulin sensitivity tests were present in almost all of our patients in whom these studies were conducted Clinical hypoglycemia that is when the disturbance in carbohydrate metabolism constituted a clinical problem was present in approximately one third of the patients Desoxycorticosterone acetate and salt exercised no effect on the impaired carbohydrate metabolism, while whole cortical extract resulted in some improvement in the blood sugar level and on the height of the glucose tolerance curve This compound too exercised some protective effect although not very marked against the development of hypoglycemia The treatment of the patients with a tendency to hypoglycemia

then involves not only frequent feedings of a high carbohydrate high protein diet but also the use of carbohydrate fraction such as cortisone in conjunction with desoxycorticosterone or whole adrenal cortical extract

In the light of the relationship of the adrenal cortex to carbohydrate metabolism the association of diabetes mellitus with Addison's disease must of necessity be rare. Of course there is no reason why a patient with diabetes should not develop Addison's disease and when this occurs the course of the diabetes is modified considerably. The development of diabetes during the course of Addison's disease however is an exceedingly interesting and in a sense paradoxical phenomenon.

At least 26 cases including 2 of our own of the association of these two diseases are recorded in the literature. Of these postmortem examination was performed in 17[113,114]. If one includes 2 instances in which no clinical diagnosis of Addison's disease was made although the adrenals were completely destroyed there are 8 instances in which the onset of diabetes mellitus and Addison's disease was simultaneous. In 5 the onset of Addison's disease preceded the diabetes and in 13 the diabetes was noted first. In the 17 examined at postmortem atrophy or fibrosis of the adrenal was observed in 12 and tuberculosis in 5. This incidence of atrophy or fibrosis is greater than that noted generally in patients with Addison's disease. Simpson has suggested that in a number of these patients a common etiologic agent exists possibly infections that results in simultaneous fibrosis of the adrenal and pancreas.

Illustrative Case

This was a white man of forty two years of age a motorman by occupation who had marked weakness fatiguability gastrointestinal symptoms hypotension and pigmentation of three years duration. The diagnosis of Addison's disease was established at another hospital after careful and adequate study. Blood sugar determinations during this initial period were relatively low. He was treated with salt and cortical extract and responded well. Two years after the onset of the symptoms of Addison's disease the patient rather suddenly developed polydypsia polyphagia and urinary frequency. Urinalysis revealed the presence of a considerable glycosuria and the fasting blood sugar level was now found to be elevated. One year after the onset of the symptoms of diabetes he was admitted to the Mount Sinai Hospital for study. He presented the typical clinical picture of Addison's disease. The blood pressure was 90/50 millimeters of mercury the blood sodium was 138 milliequivalents per liter while the chlorides were 95.2. The urea nitrogen was 12 milligrams per cent. The hemoglobin was 109 per cent and the red blood cell count was 5.8 million per cubic millimeter. The fasting blood sugar level was 150 mgm per cent and there was a trace of sugar in the urine. An oral glucose tolerance test employing 1.75 grams per kilogram of body weight revealed a typical diabetic curve

	Blood Sugar mgm %	*Urine Sugar %*
Control	150	trace
½ hour	280	1.1
1 hour	300	3.3
1½ hours	320	4.0
2 hours	380	3.3
3 hours	320	4.8
4 hours	250	4.6

In order to establish the diagnosis of Addison's disease independently of the history a salt deprivation test was performed. Seventy two hours after the withdrawal of salt and extract the patient manifested early evidence of acute adrenal insufficiency. The blood sodium had fallen to 119.1 milliequivalents per liter and the chlorides to 82.8. The blood urea nitrogen had increased to 36 milligrams per cent while the hemoglobin had risen to 115 per cent with a proportionate increase in the hematocrit. It was evident that the patient had definite adrenal cortical insufficiency and treatment with salt and cortical extract was resumed.

During the remainder of his stay at the hospital it was found that the diabetes could be readily controlled with small amounts of insulin. Ten units of protamine zinc insulin daily was enough to maintain the blood sugar at normal levels and to prevent glycosuria. During the period of experimental study with insulin dosage it was found that hypoglycemic episodes could be readily precipitated. Ten units of insulin created no difficulties while 15 units often produced relatively severe hypoglycemia that required prompt treatment. The insulin requirement was somewhat less when the patient was maintained on salt alone or on salt with desoxycorticosterone while it was slightly increased when whole adrenal cortical extract was used for the treatment of Addison's disease. Similar observations were noted by other authors who conducted like studies[8, 81, 9]

TABLE 14 —PATIENTS WITH ADDISON'S DISEASE WHO SUBSEQUENTLY DEVELOPED DIABETES MELLITUS

Author	*Sex*	*Age*	*Pathologic Diagnosis*	*Daily Insulin Requirement (Units)*
Rhind and Wilson (1941)[88]	F	32	Atrophy	48–60
Thorn and Clinton (1943)[89]	M	23	?	10–25
Soffer (1945)	M	42	?	10
Lowrie[113]	F	30	?	5
Simpson[113]	M	20		26

TABLE 15 —PATIENTS WITH SIMULTANEOUS DIABETES MELLITUS AND ADDISON'S DISEASE

Author	*Sex*	*Age*	*Pathologic Diagnosis*	*Daily Insulin Requirement (Units)*
Arnett (1927)[85]	F	39	Atrophy	20–30
Levy Simpson (1932)	M	16	Atrophy	Less than 10 units
Gowen (1932)[86]	F	54	Atrophy	Less than 5 units
Nix (1943)[87]	M	39	Atrophy	
Ogle[113]	M	55	Tuberculosis	0 (No Addison's disease noted during life)
Montgomery[113]	M	45	Tuberculosis	0 (No Addison's disease noted during life)
West[113]	M	55	Tuberculosis	0
Rabe[113]	M	45	Tuberculosis	

In an analysis of the cases reported in the literature one is impressed with the fact that after the development of diabetes the course of this latter disease is considerably modified. The hyperglycemia and glycosuria are

reduced, while the insulin requirement is lessened. This is essentially what is to be expected in view of the relation of the adrenals to carbohydrate metabolism. The marked sensitivity to insulin characteristic of the patient with adrenal cortical destruction and of the bilaterally adrenalectomized animal persists. The administration of insulin slightly in excess of the amount required for control of the diabetes may precipitate hypoglycemic episodes. Thus in 15 cases including our own of the association of both diseases, in 9 there is specific mention of pronounced insulin sensitivity, while 2 patients actually died of hypoglycemic shock.[59, 60, 61, 6, 6, 66, 68, 69]

TABLE 16.—PATIENTS WITH DIABETES MELLITUS WHO SUBSEQUENTLY DEVELOPED ADDISON'S DISEASE

Author	Sex	Age	Pathologic Diagnosis	Daily Insulin Requirement (Units): Before Development of Addison's disease	Daily Insulin Requirement (Units): After Development of Addison's disease
Unverricht (1926)[4]	M	32	Tuberculosis	40	5
Umber (1928)	F	52	Tuberculosis	—	—
Rowntree and Snell (1931)[4]	*M*	24	Atrophy		*30*
Rowntree and Snell (1931)	M		Atrophy	—	—
Rogoff (1936)[1]	M	45	Atrophy? Following denervation of adrenals	48 60	5 10
Bloomfield (1939)	M	30	?	40	[illegible]
McCullagh (1942)[6]	M				
Bowen, Koepf, Kessel and Hall (1942)	F	70	Tuberculosis	0	0
DeWitt and Murphy[113]	F	25	Fibrosis	30	10
Bernstein[3]	M	44	Fibrosis	56	4
Simpson[113]	M	47	Atrophy	[illegible]	[illegible]
Armstrong	M	35		56	Less than 6 units
Adler (Mount Sinai)	F	25	?	55	5

Renal Function in Addison's Disease.—During acute Addisonian crisis there is temporarily a marked impairment of renal function related to the dehydration, reduction in blood volume and blood pressure, and shock. This is usually associated with an elevation in the blood urea and non protein nitrogen and hyperproteinemia. The administration of adrenal cortical extracts and intravenous saline results in improvement which keeps pace with the general clinical improvement. This temporary impairment of renal function is similar to that observed in dehydration and shock from any cause, bears no specific relationship to Addison's disease, and is extrarenal in origin.

The question, however, as to whether Addison's disease *per se* may produce impairment of renal function is a difficult one to answer. Structurally, necropsy findings usually fail to reveal any consistent abnormal anatomic changes. Guttman[7] in a statistical analysis of 566 autopsied cases of Addison's disease collected from the literature found that less than 10 per cent showed morphologic changes in the kidneys sufficient to justify an anatomic diagnosis of renal disease. Barker[8] reported somewhat dif-

ferent findings. Of 28 cases which were studied pathologically, 10 showed definite renal anatomic changes. The change most prominently observed was that of a tubular atrophy which consisted of a flattening of the epithelium and diminution of the amount of cytoplasm. The tubular lumens appeared diminished in diameter with intertubular edema. Barker felt that these changes were due to the hypotension and anoxemia. Talbott and his group[45] reported on the pathologic findings in 6 instances of Addison's disease in which renal anatomic studies revealed no abnormalities. This is similar to the results observed in experimentally adrenalectomized animals in which no significant histologic changes are evident in the kidneys.[46]

We can conclude therefore that patients dying from Addison's disease generally do not show any consistent or significant alterations in renal structure. The fact that structural changes are not evident, however, does not necessarily mean that there may not be alterations in renal function *specifically related to Addison's disease. This phase of the problem could* be studied with advantage only during the intercritical periods when the extra-renal factors mentioned above which occur during crisis do not play a significant role.

Examination of renal function with routine clinical procedures such as the determination of maximum specific gravity, albuminuria, the presence of red blood cells and casts in the urinary sediment, the concentration of non-protein nitrogen in the serum and phenosulphonphthalein excretion do not usually reveal any constant deviation from the normal in patients with Addison's disease in periods between crises. More elaborate procedures specifically and sensitively testing glomerular filtration and tubular absorption are required to determine the presence or absence of mild impairment of renal function in this illness. Such studies were undertaken and reported upon by Talbott and his group[4] in an excellent paper on renal function in 10 patients with Addison's disease during intercritical periods when the patients were well, had a normal blood electrolyte pattern and were maintained only on supplementary oral salt therapy. The rate of formation of glomerular filtrate was determined by inulin clearance and was found to be definitely below normal in every instance. When the test was repeated following the administration of desoxycorticosterone acetate there occurred a significant increase in the rate of formation of glomerular filtrate, although the degree of restoration was not to normal levels. The use of whole adrenal cortical extract (Wilson) did not yield results beyond those achieved by the desoxycorticosterone acetate. The question arises as to whether the depression of the rate of glomerular filtration may not be due to the reduction in renal blood flow such as occurs in Addison's disease. The results obtained with the creatinine clearance and with diodrast clearance at low iodine plasma levels suggests that the depression of rate of glomerular filtration is out of proportion to the reduction in renal blood flow. Their observations on the maximum ability of the tubules to excrete diodrast and reabsorb glucose suggests that the tubular excretory function is well maintained while their ability to reabsorb, at least as far as glucose is concerned, is seriously impaired.

The relationship of renal function to water, sodium and potassium clearance is a matter of great interest and importance Talbott and his group[1] found that there was no significant change in tubular reabsorption of water either before or after administration of desoxycorticosterone acetate or whole adrenal cortical extract Similarly no dissipation of sodium was apparent while there occurred a definite increase in potassium excretion following treatment with potent cortical extracts This increase in excretion of potassium was produced mainly by an increase in glomerular filtration These results are in contrast to the results obtained in the experimentally adrenalectomized animal by Harrison and Darrow[47] who found that the renal tubules cannot absorb adequate quantities of sodium in adrenal insufficiency while the clearance of potassium is decreased Specific treatment restored the values for these clearances to normal These would seem to be reasonable conclusions in view of the nature of the electrolyte changes which occur in adrenal insufficiency and the effect of hormonal therapy on the blood electrolyte pattern

It is at present hazardous to draw too many and too definite conclusions concerning renal function in Addison s disease There are too many gaps in our knowledge, particularly in bridging the information obtained in adrenalectomized animals to analogous situations in Addison s disease The patient between crises and without therapy does not lend himself too readily to prolonged and difficult studies while during therapy this factor introduces a distortion in our findings It would seem safe however to draw the following conclusions The renal function in patients with Addison s disease does not constitute for all intents and purposes a particularly serious clinical problem The ordinary procedures testing renal function and the autopsy findings are usually normal There is however some impairment of the rate of glomerular filtrate formation of the tubular capacity to reabsorb water and sodium while there is a diminished tendency for the tubules to excrete potassium These changes are to a considerable extent rendered reversible by specific hormone therapy

Liver Function in Addison s Disease —In view of the nature of the carbohydrate disturbance in Addison s disease with its dependent depletion of hepatic glycogen one might suppose that liver function is impaired in these cases Rowntree and Snell[3] investigated the status of hepatic function in their patients with Addison s disease by determining the serum bilirubin content and by the ability of the liver to excrete injected bromsulphthalein The serum bilirubin levels were uniformly normal but the results of bromsulphthalein tests indicated the presence of some impairment of liver function Thorn Dorrance and Day[6] used the intravenous hippuric acid test in 9 patients and found values below normal in all instances In none of these cases were there any evidences of impaired renal function

The Urinary Excretion of 17 Ketosteroids in Addison s Disease —The 17 neutral ketosteroids, as indicated elsewhere in this book arise from substances produced by both the adrenal glands and the male gonads The β fraction originates from the cells of the adrenal cortex while the α fraction is manufactured by these cells and by the gonads The normal range for urinary excretion of the 17 ketosteroids in adult males is 12 to 20 milligrams and in females 10 to 16 milligrams per twenty four hours In

Addison's disease this value is usually tremendously decreased the total urinary excretion of the 17 ketosteroids usually being well below 5 milligrams for a twenty four hour period and frequently entirely absent from the urine[45] Essentially the same is true of the glycogenic corticoids In the presence of destruction of the adrenals the urinary corticoids are markedly reduced and occasionally absent An exception to these findings is noted in the cases of adrenal insufficiency associated with congenital adrenal cortical hyperplasia In these instances the urinary excretion of the neutral 17 ketosteroids is increased and the urinary excretion of the glycogenic corticoids is normal

Blood Counts —The blood count in this disease does not present any very unusual features There is usually observed a mild secondary anemia normocytic in character with a relative increase in lymphocytes The red blood cell count rarely falls below 3 0 million During crisis when there is marked dehydration and hemoconcentration there is a misleading increase in the blood cellular elements and hemoglobin which falls rapidly with active therapy and increase in hydration There is usually a low normal total white count associated with a lymphocytosis and a modest eosinophilia

Basal Metabolic Rate —*In most patients with Addison's disease the* basal metabolic rate is moderately depressed rarely however falling below −15 to −20 per cent of the normal standard Treatment with specific hormones produces only a slight increase in the basal metabolic rate probably due to an increase in the general well being of the patient rather than to any specific endocrine effect of the hormone Thorn[8] found that in 35 out of 55 patients all of whom were receiving treatment with desoxycorticosterone acetate the basal metabolic rates varied between +10 and −10 per cent of the standard In 6 patients the values exceeded +10 per cent and in 14 the level was below −10 per cent Values of −25 per cent or less usually indicate the presence of considerable thyroid or pituitary deficiency Occasionally very low basal metabolic rates are observed just before the development of adrenal crisis The I^{131} accumulation gradient and the serum protein bound iodine level are usually within the normal range although the mean are somewhat less than that encountered in normal individuals[117]

X ray Diagnosis of Addison's Disease —Roentgenologic demonstration of calcification of the adrenals is sometimes a helpful aid in the diagnosis However the technic is a difficult one and the results may be misleading because of the frequent presence of calcified rib cartilages overlying the adrenals and the occasional presence of calcified lymph nodes in the region of the adrenals However if one can be certain that the observed calcification is in the adrenals the tuberculosis origin of the Addison's disease can be made with certainty The absence of *x* ray evidence of adrenal tuberculosis has no diagnostic value

The Heart in Addison's Disease —It has been observed repeatedly that patients with Addison's disease have a limited myocardial reserve Mild effort is associated with considerable dyspnea and cardiac palpitation It *is interesting to note* however that prior to treatment with desoxycorticosterone acetate frank signs of heart failure such as pulmonary edema and hepatic and venous engorgement were practically never seen A possible

explanation for the lack of the more striking features of heart failure may reside in the fact that the incapacitating character of the illness is such that the patients are in a perpetual state of rest and the cardiac burden is thus automatically reduced to a minimum.

The smallness of the size of the heart in Addison's disease and the flabby and thin character of the musculature have been commented upon frequently.[3] The electrocardiogram in many of these patients shows changes suggestive of myocardial disease.[48, 49] The electrocardiographic tracings



Fig 14.—Electrocardiographic tracing in an untreated patient with Addison's disease. Note marked bradycardia and isoelectric T wave in all leads.



Fig 15.—Following several weeks of treatment with desoxycorticosterone, whole adrenal extract and salt. Note increase in heart rate and increased amplitude of T waves in lead I and II.



Fig 16.—Four years after beginning of therapy. Note essentially normal electrocardiographic tracing.

usually show a low voltage in all leads, low isoelectric or diphasic T waves in all leads, less frequently prolongation of the ST interval and occasionally inversion of T_1, T_2 and frequently T_3 and T_4. Oddly enough, as Thorn, Dorrance and Day[6] have pointed out, treatment with desoxycorticosterone acetate not infrequently results in progressive electrocardiographic evidence of myocardial injury. This may be due to the increase in the size of the heart which results from this therapy[50, 51] and the increase in blood pressure and circulating blood volume. The flabby cardiac musculature may find it difficult to cope with the rather sudden increase in its burden. Excessive

dosage with this hormone has resulted in overt heart failure as has been reported by Ferrebee,[8] ourselves[25] and Willson[63]

Occasionally a marked bradycardia is noted during or just before the onset of crisis It is interesting to speculate as to the relationship of the elevated blood potassium to this abnormality in rhythm That abnormalities in cardiac rhythm can be produced by potassium salts in the experimental animal and in humans is now well recognized Nicholson and Soffer[64] have observed the development of slow auricular fibrillation in adrenalectomized dogs during insufficiency and while the serum potassium was considerably elevated Patients in Addisonian crisis never develop an elevation of serum potassium comparable to that of the adrenalectomized dog but a considerable and prolonged increase in serum potassium frequently does occur which may play a part in the production of the bradycardia

Of interest are the experimental myocardial changes found associated with diets deficient in potassium In 1937 Schrader and his group[106] described pathologic changes in the heart and other organs of rats placed on a low potassium diet These cardiac observations were subsequently confirmed by Thomas and his coworkers[107] and by Follis and his group[108] The hearts of the rats placed on potassium deficient diets were somewhat hypertrophied and histologically showed areas of necrosis of the muscle fibers with destruction and disappearance of the nuclei Associated with these changes there was a considerable infiltration of leukocytes around the involved regions In the early stage the cellular infiltration consisted essentially of polymorphonuclear leukocytes later mononuclear phagocytes predominated There was apparently no involvement of the blood vessels and no perivascular accumulations of cells Healing eventually occurred with considerable scarring On the basis of these carefully controlled studies the myocardial changes in these animals could be justly attributed to the dietary deficiency in potassium and Follis and his coworkers[108] found that the potassium content of the heart muscle of their rats was 35 per cent lower than that of the control animals

In 1942 Darrow and Miller[109] produced cardiac lesions in rats by repeated injections of large amounts of desoxycorticosterone acetate These lesions could not be distinguished from those produced by diets deficient in potassium It would seem then that the desoxycorticosterone acetate exercised this effect essentially by lowering the blood and organ content of this ion Finally Goodof and MacBryde[110] reported a case of Addison's disease treated with desoxycorticosterone acetate in which death was caused by cardiac failure At autopsy the Addison's disease was found to be due to primary atrophy of the adrenals and foci of necrosis were found in the musculature of all four chambers of the heart These necrotic areas were similar to those observed in animals which had received large amounts of desoxycorticosterone and diets deficient in potassium

This observation may be of considerable therapeutic importance in that it emphasizes the need for caution in the dietary and hormonal treatment of patients with Addison's disease Although a low potassium diet is essential in the treatment of the patients when they do not receive desoxycorticosterone or receive this hormone in only minimal amounts such dietary

restriction may be hazardous where the synthetic hormone is exhibited in adequate quantities

In our own experience both treated and untreated patients with Addison s disease frequently show histologic changes in the heart muscle characterized essentially by degeneration of the muscle fibers occurring in diffuse patches, but unassociated with leukocytic infiltration In one instance in particular where death occurred suddenly these changes were very striking This patient had been treated with desoxycorticosterone and was progressing very satisfactorily when death occurred suddenly within the space of several minutes Analysis of the heart blood just before death revealed a normal blood electrolyte pattern and a normal blood sugar level At necropsy, profound atrophy of both adrenals was found In addition the heart muscle was the seat of an extensive change characterized by a diffuse myolysis of the heart muscle in which the muscle fibers had virtually disappeared in many areas and only the surrounding fibrous capsules were left The nuclei were in various stages of karyolysis and in many instances had entirely disappeared However, there were no evidences of any inflammatory reaction or leukocytic infiltration The coronary vessels were perfectly patent and showed no arteriosclerotic changes

Summary of the Laboratory and Clinical Findings in Addison s Disease — The diagnosis of Addison s disease is based on certain very definite clinical and laboratory findings In few diseases is the clinical picture so clearly defined, and its classical pattern so consistently followed All patients with Addison s disease have asthenia gastrointestinal symptoms pigmentation, and hypotension at some time during the course of their illness Usually there is in addition a considerable loss in weight About 10 or 15 per cent of the patients show a decided craving for salt a somewhat smaller percentage are inordinately fond of foods rich in carbohydrates The disease is further characterized by the development of periods of crisis These are episodes of dehydration and shock of a most critical character During these periods there occurs a marked intensification of all the symptoms Nausea and vomiting become intractable and the asthenia profound The blood pressure falls to unobtainable levels the body temperature is lowered and the pigmentation assumes a darker hue There is usually ample warning before the on et of the acute crisis For a number of days before the patient will notice an increase in nausea with perhaps some vomiting and diarrhea The weakness will become more pronounced and there will be a gradual fall in blood pressure Mental irritability frequently becomes a pronounced symptom at this time This comparatively moderate increase in intensity of the symptoms may continue for several days until the patient precipitately develops symptoms of the acute and frightening character of shock It must be remembered that the Addison ian crisis is a critical episode and associated with a very high mortality rate It calls for immediate and vigorous therapy The crises are usually induced by cessation of therapy acute infections gastrointestinal disturbances minor and major surgical procedures early pregnancy undue effort and hot weather when excessive diaphoresis causes an additional loss of salt and hypoglycemic episodes

About one quarter to one half of the patients with Addison's disease develop hypoglycemic episodes. These are entirely independent of the state of well being of the patient or the blood electrolyte pattern. They can vary in severity from mild hunger symptoms to actual coma, although the latter occurs only rarely. It is essential that measures be employed to combat the hypoglycemic state, since the tendency to spontaneous recovery is markedly reduced in these patients. The Addisonian patient too is unusually sensitive to drugs like insulin, thyroid extract, morphine and other agents producing narcosis. Insulin ought never to be employed in these patients except for the treatment of concomitant diabetes, and the other drugs with the greatest caution.

The significant laboratory findings in Addison's disease center essentially about the blood and urine electrolytes. During acute adrenal cortical insufficiency there is a marked excretion of sodium and chloride in the urine, a pronounced drop in the blood concentration of these ions, a diminution in plasma bicarbonate, and an increase in the serum potassium. There is considerable hemoconcentration with an increase in total protein and retention of blood nitrogenous elements. Occasionally, the fasting blood sugar level is lowered. More frequently oral glucose tolerance tests will reveal a flat curve with a tendency to a hypoglycemic dip two to three hours after the ingestion of glucose.

During periods of well being, the so-called "intercrisis" phase, the blood electrolyte pattern may show very little deviation from the normal. Under such circumstances salt deprivation tests will bring out the underlying disturbance in the electrolyte pattern. These tests can precipitate patients into adrenal failure and must be performed with caution.

Hypoadrenia.—Within recent years there has been a tendency to speak of hypofunction of the adrenal cortex. This clinical entity apparently refers to that large group of patients of asthenic habitus who are chronically tired, constipated, and have low blood pressure. Their basal metabolic rates are frequently lowered. The tendency has been to treat these patients with adrenal cortical extract. This practice is to be severely condemned. There is no evidence, either laboratory or clinical, that would justify the conclusion that the symptoms of these patients are due to adrenal cortical underfunction. The indiscriminate use of potent extracts may result in harm. It is at least theoretically possible that the prolonged use of adrenal hormone may result in some atrophy of the adrenal cortex.

DIFFERENTIAL DIAGNOSIS

There are several groups of diseases and some sets of circumstances in which the clinical picture produced may simulate to varying degree, and must be differentiated from Addison's disease.

1. **Racial Differentiation.**—There are certain racial groups who are normally dark skinned and who frequently present oral pigmentation. This is particularly true of Ethiopians, Levantines, Latins, Orientals and American Indians. In attempting to determine the significance of pigmentation in a given patient it is always wise to investigate the antecedents

of the patient if possible. It may be very informative to note that one or both parents or other siblings of the patient are equally pigmented.

2. **Undue Exposure to Sun.**—This usually produces pigmentation of the skin and the pigment deposited in the skin is melanin. Many patients with Addison's disease will comment upon the fact that the first evidence of unusual pigmentation was the failure of a summer tan to subside. However, the patient with a simple sunburn does not present the general physical appearance, nor does he have the signs and symptoms which may be confused with Addison's disease. If there is doubt, suitable laboratory studies such as blood electrolyte determinations, salt deprivation tests or the eosinophil response to ACTH will help clarify the diagnosis.

3. **Endocrine and Metabolic Diseases.**—(*a*) Hyperthyroidism with pigmentation will sometimes cause confusion. The presence of the clinical picture of Graves' disease with sweating, exophthalmos, high basal metabolic rate and high pulse pressure will usually make the differentiation clear.

(*b*) Myxedema with pigmentation is differentiated from Addison's disease by the fact that these patients usually gain weight or at least maintain their weight, are terribly sluggish, the skin is very dry, frequently thickened, and they have an unusually low basal metabolic rate. Their normal blood electrolyte pattern and their satisfactory response to small doses of thyroid extract or thyroxin usually establishes the diagnosis of myxedema.

(*c*) *Simmonds' Disease.* *These cases may cause considerable confusion* with Addison's disease, due probably to the fact that with atrophy or destruction of the anterior lobe of the hypophysis there occurs some actual atrophy of the adrenal cortex with some symptoms of adrenal cortical underfunction. However, these cases are not true instances of Addison's disease. They usually present the picture of marked weight loss, asthenia and hypotension. Not infrequently they have some pigmentation and mild gastrointestinal disturbances. However, the basal metabolic rate in Simmonds' disease is very low, the pigmentation is never marked, typical Addisonian crises generally do not occur, and the blood electrolyte pattern is usually within normal range. The patient with Simmonds' disease may show some evidence of adrenal cortical insufficiency with the various salt deprivation tests, but never to the critical extent observed in Addison's disease. The eosinophilic response of this group of patients to a test dose of ACTH is usually superior to that observed in patients with Addison's disease. The differential diagnosis is further aided by the diffuse polyglandular involvement noted in Simmonds' disease and the mild, relatively unsatisfactory response to specific therapy with salt and adrenal cortical extracts.

(*d*) Hemachromatosis. The pigments deposited in the skin in this condition are hemofuchsin, an iron free pigment, and hemosiderin, an iron containing pigment. Melanin is never found present. In addition, the presence of a large, hard, nodular liver, and glycosuria and hyperglycemia usually renders the diagnosis clear.

4. **Pigmentation Due to Poisoning With Heavy Metals.**—Chronic arsenic poisoning, extensive and prolonged bismuth therapy, and argyria may produce skin pictures superficially similar to that observed in Addison's disease. The history of arsenical therapy, the presence of keratosis and

the absence of the other signs and symptoms of Addison's disease help to differentiate the two conditions. Bismuth usually produces oral pigmentation alone and then in the form of a rather characteristic "bismuth line." The pigmentation of argyria is characterized by the presence of a bluish or slaty overcast and the history of treatment with silver nitrate or silver protein salts usually suggests the correct diagnosis. Proper laboratory studies and biopsy of a pigmented area will conclusively eliminate the diagnosis of Addison's disease.

5. **Wasting Diseases.**—Intra-abdominal malignancy with skin pigmentation (acanthosis nigricans) may cause some confusion in the differential diagnosis. The presence of an intra-abdominal mass or evidence of malignant metastasis and cutaneous biopsy is usually conclusive.

Miscellaneous Diseases.—Scleroderma with pigmentation can be differentiated from Addison's disease by the presence of the typical changes in the skin in the former disease. The presence of a normal blood electrolyte pattern and the normal response to the various tests of adrenal cortical function serve conclusively to delimit the diagnosis.

Pellagra can only remotely be confused with Addison's disease. The localized nature of the skin discoloration, most marked in the hands and wrists, the coarse nature of the affected skin, the characteristic appearance of the tongue, the mental changes, the persistent diarrhea, and finally the response to treatment with nicotinic acid should establish the diagnosis of pellagra.

The dehydration and salt wastage associated with the late stages of glomerulonephritis may at times result in a clinical picture that may bring to mind Addison's disease because of the electrolyte losses. The differential diagnosis, however, can easily be made on the basis of the renal findings.

Finally, neurasthenia must be differentiated from Addison's disease. These patients will complain of marked weakness and anorexia; they will frequently have low blood pressure and a low basal metabolic rate. However, they are not pigmented. A definite history of recurrent anxiety episodes and the frequent presence of various conversion symptoms will suggest the proper diagnosis. In instances where there is doubt, blood electrolyte studies, glucose tolerance curves, salt deprivation tests and eosinophilic response to ACTH will serve to eliminate the presence of Addison's disease.

Within recent years there has been a tendency to classify patients with psychasthenia as instances of adrenal cortical underfunction. There is no justification for this grouping. These patients have neither the typical clinical features nor the characteristic electrolyte disturbances which are to be expected in adrenal cortical disease. Treatment with supplementary salt with or without cortical extract produces no permanent improvement in their clinical condition. The satisfactory transitory response which is sometimes observed is due to the suggestive effect of any new therapy. The use of potent hormonal products like desoxycorticosterone or whole adrenal cortical extract is by no means entirely innocuous and should be avoided except in those instances in which the clinical indications are clear cut. The anxiety psychoneurotic states do not belong to this category.

SUPRARENAL APOPLEXY, SPONTANEOUS SUPRARENAL HEMORRHAGE, PURPURA FULMINANS (WATERHOUSE-FRIDERICHSEN SYNDROME)

The earliest recorded instance of the association of fulminating purpura with bilateral adrenal hemorrhage is probably the report of Voelcker[70] which appeared in the pathologic reports of the Middlesex Hospital in England in 1894. Several years later Garrod and Drysdale,[71] Batten[72] and Talbot[73] noted similar instances. In 1901, Little[4] in a most illuminating report recognized the association of the fulminating purpura and adrenal hemorrhage as constituting a distinctive clinical entity. The first comprehensive summary of the then available literature was by Waterhouse[74] in 1911. He collected 15 cases from the literature, added 1 of his own and pieced together a definite clinical picture. He speculated concerning a possible bacterial cause for the disease, although five years earlier in 1906 Andrews[5] had succeeded in isolating the meningococcus from the blood of an adult who died of acute bilateral adrenal hemorrhage. In 1918 Maclagen and Cooke[6] also recovered the organism from the blood of a young adult. In 1918 the second comprehensive review of this disease was reported by Friderichsen.[77] Since then many scattered individual cases have been added to the literature with excellent reviews by Aegerter,[78] Sacks,[79] and Kunstadter.[80]

To date approximately 150 cases have been reported and the disease has assumed a fairly clear cut form. Various well-defined causative factors have been established depending essentially on the age group of the patient. The illness is mostly a disease of childhood, particularly under the age of two years. Within recent years, however, many instances of the illness in adults have been recorded.[9, 93] In 1944 Martland,[94] in reviewing his experience in the medical examiner's office, found 19 instances of this disease in over 10 000 autopsies performed over a period of thirteen years. Ten of the subjects were infants and children, mostly below the age of five, and 9 were adults. All presented the classical clinical features of cyanosis, purpura, petechiæ and bilateral massive adrenal hemorrhage without gross meningitis.

Etiology.—Minute to moderate sized adrenal hemorrhages may occur during the course of acute infectious diseases such as measles, diphtheria, scarlet fever, typhoid fever, *etc.*, as well as in blood dyscrasias such as leukemia, hemophilia and purpura, during the course of neoplastic disease and in peritonitis following intraabdominal procedures. However, the amount of adrenal hemorrhage which occurs under these circumstances is not extensive enough to produce any evidences of adrenal failure and is of dubious clinical significance.

The instances of massive adrenal hemorrhage fall essentially into two groups: (1) in the newborn infant, and (2) in older children and adults. The responsible etiologic factors are different in the two categories and there are some *clinical variations*. *Adrenal hemorrhage in the newborn* results most frequently from trauma incidental to a difficult and prolonged labor. Asphyxia, the use of forceps and violent resuscitative measures are

frequently responsible. Fairly extensive adrenal hemorrhage has been observed in hereditary syphilis of the newborn[81] and when the mother developed a toxemia of pregnancy such as eclampsia.[82]

In older children and in adults adrenal apoplexy usually occurs in association with an acute fulminating sepsis. In most instances in which bacteriologic studies were conducted the overwhelming sepsis was due to a massive invasion by the meningococcus. The onset of the disease is so sudden and its course so rapid that adequate bacteriologic investigations have been made only infrequently. However, in a study of the literature there are at least 30 instances in which the meningococcus has been recovered from the blood either during life or directly after death. Sacks[79] found this organism to be the responsible agent in 60 per cent of the cases, while in the remaining 40 per cent either the blood cultures were negative or growths of streptococcus hemolyticus were obtained. Kunstadter's review,[80] which was of a somewhat later date, assigned the etiologic role to the meningococcus in 65 to 70 per cent of the reported instances. Firor,[83] in reviewing the cases of adrenal hemorrhage observed in the Harriet Lane Home of the Johns Hopkins Hospital, reported that they occurred during the course of staphylococcus septicemia and streptococcus viridans endocarditis.

In the older literature a host of different organisms was incriminated as the offending agent. These included, in addition to those already mentioned, the pneumococcus, colon bacillus, bacillus pyocyaneous and bacillus Friedlander. These organisms were cultured from the blood, skin lesions and adrenals. It is entirely possible that any of this group of organisms may conceivably have produced the sepsis with the adrenal hemorrhage, but the nature of the organisms suggests the possibility that they may have been either contaminants or secondary invaders.

Martland[84] is of the opinion that all cases of the Waterhouse-Friderichsen syndrome are due to massive invasion with meningococci, and he advances cogent arguments to support his thesis. He emphasizes the frequency of this disease during those months (March, April, May) when meningococcic infections are most prevalent. He points out that the gross pathologic changes observed are characteristic only of a fulminating meningococcal septicemia without meningitis. Finally, in his extensive experience with all types of infections due to streptococci, staphylococci, pneumococci and other organisms he has never observed bilateral massive adrenal hemorrhage in any of these infections or in any condition other than fulminating meningococcemia.

Pathology.—The outstanding pathologic finding is extensive bilateral adrenal hemorrhage. The adrenals may be the seat of innumerable minute hemorrhagic areas, or the whole adrenal may be converted into one bloody mass. Rarely the hemorrhage ruptures through the adrenal capsule into the peritoneal cavity. Four such cases in the newborn were reported by Arnold.[84] The zona reticularis of the cortex is usually the site of the greatest degree of hemorrhage, the other layers apparently being involved subsequently by diffusion. Not infrequently a rim of cortex in the zona glomerulosa is left intact. The presence of thrombosis of the suprarenal vein has been reported on several occasions.[87, 85] Whether this was primary

or secondary to the hemorrhage it is of course impossible to say. The fact that it occurs relatively infrequently would suggest that when present it plays a secondary role in the pathogenesis of the adrenal hemorrhage. No such suprarenal vein thrombosis was observed in any of the cases studied by Martland. It should be emphasized that a similar clinical picture may occur in acute meningococcemia and in other severe acute infections in which no massive hemorrhages are found in the adrenals. In these instances the adrenal cortical cells may show extensive histological changes.

The skin lesions are due to widespread destruction of the capillaries and arterioles either as a result actually of bacterial embolization or perhaps due to the toxins liberated by the organisms. Brown[86] found a perivascular leukocytic infiltration around the capillaries and arterioles of the skin in instances of meningococcus sepsis. Microscopic examination of the skin of two of the patients in our series showed extravasations of blood beneath the epidermis. All the capillary branches contained clotted fibrin with clumps of gram negative cocci.

In view of the fact that most cases are due to meningococcemia one might expect to find extensive involvement of the meninges. On pathologic studies this proves not to be the case. Examination of the brain reveals only a congestion of the vessels of the leptomeninges. There may be evidence of increased intracranial pressure such as flattening of the convolutions over the brain surface. Occasionally there is evidence of encephalitis. Only rarely has actual meningitis been described. The reason for the infrequency of this complication probably resides in the rapidity of the clinical course. Death usually occurs so early that there is no time for the development of a purulent meningitis.

Rabinowitz[87] and Bamatter[88] have called attention to the frequent occurrence of an enlarged thymus and hyperplasia of the intra-abdominal lymphoid tissue in association with adrenal hemorrhage. In his review Sacks[79] states that in 10 instances there was specific mention of enlargement of the thymus while 16 cases were reported to show considerable hyperplasia of Peyer's patches, mesenteric lymph nodes and solitary lymphoid follicles of the intestines. Bamatter[88] considers this thymolymphatic prominence of significance in the pathogenesis of the disease, particularly in view of the association of status thymolymphaticus with adrenal hypoplasia.

The other organs of the body show those changes which one would expect in the presence of an acute sepsis. There is cloudy swelling of the parenchymatous viscera; the spleen is usually enlarged, soft and congested, presenting the picture of an acute splenic tumor. There may be terminal pulmonary edema.

Exclusive of the cases reported in the literature we have had occasion to study the records of 5 patients with the classical Waterhouse-Friderichsen syndrome who were observed at the Mount Sinai Hospital. One child was ten years of age and the remaining 4 children varied from four months to three years of age. In 4 of the 5 cases the meningococcus was cultured from the blood stream while in 1 instance no organism could be isolated. Two of the 5 patients showed considerable thymic enlargement with visceral lymphadenopathy. One of these children was ten years

old and the other eight months old In a third instance in a child of one and one-half years there was marked hyperplasia of Peyer's patches None of the 3 patients had any pathologic evidence of a purulent meningitis All showed the typical extensive petechiae and cutaneous purpura

Symptoms and Clinical Picture — The disease pursues a fulminating usually rapidly fatal course and is characterized essentially by the features of an overwhelming sepsis with extensive cutaneous petechiae and purpura and finally circulatory collapse Death usually occurs within twenty four hours after the onset of the significant symptoms Recently two instances of the disease were reported in adults with survival periods of eighty and eighty-eight hours respectively [9] The disease may appear suddenly in a previously healthy child or adult or it may be preceded by the symptoms of a mild upper respiratory infection or apparently innocuous gastrointestinal disturbance The early symptoms are those of irritability malaise headache diffuse abdominal pains vomiting and diarrhea The initial pyrexia may be relatively moderate but as the disease progresses it becomes rapidly higher and in one reported case reached 108 F In one of the patients in our group the maximum temperature peak was 107° F The usual temperature level varies from 104° to 105° F The alarming elevation of the temperature however occurs rapidly and may attain a *maximum peak within an hour or two after the onset of the disease* Occasionally the hyperpyrexia is preceded by a chill After the early irritability the central nervous system symptoms may become progressively more pronounced Headache may become intense slight stiffness of the neck is occasionally present convulsions are not uncommon and finally the patient lapses into a stuporous and comatose state which persists until death

Shortly after the onset of the disease a characteristic and striking cyanosis appears The cyanosis may be intense particularly in the dependent portions of the body which may actually appear livid especially with the superimposed purpuric eruption Occasionally varying parts of the body alternate between cyanosis and pallor The association of blueness of the skin with rapid shallow respirations which are often grunting in character and the dilation of the alæ nasæ may suggest the presence of pneumonia However physical and *x* ray examination of the chest will usually reveal that the meager pulmonary findings are hardly adequate to explain the profound clinical picture Soon after the appearance of the cyanosis a petechial eruption is noted Petechiae may be first seen in the conjunctivae or over the extremities or the trunk Very promptly however a diffuse macular purpuric rash will appear many areas of which will become confluent into large irregular patches The rash does not fade on pressure and will persist until death Just before the fatal termination of the disease circulatory collapse will ensue The temperature may fall precipitately to subnormal levels the pulse becomes barely perceptible the blood pressure unobtainable and rales appear at the lung beds The alarming and rapid course of events the dramatic appearance of the signs and symptoms and the inevitably fatal termination constitute a frightening clinical picture

Laboratory studies usually although not always reveal a moderate leukocytosis The actual white blood cell counts as reported in the literature vary from 7000 to 88 500 with an increase in granulocytes and a shift

to the left. Platelet studies have been done most infrequently and in only one instance was there a thrombocytopenia with prolongation of the bleeding time and an absence of clot retractility.[89] Spinal fluid examination usually fails to reveal any abnormalities. Rarely is there an increase in cells or spinal fluid pressure, and only infrequently was the meningococcus cultured from the spinal fluid.[78] Blood sugar determinations were performed in 4 patients by Magnusson,[90] and on 2 by Baumann.[91] In all 6 instances a marked hypoglycemia was present.

D'Agati and Marangoni[96] report the results of their laboratory studies in 6 adults with this syndrome. All of their group exhibited a considerable elevation of the non-protein nitrogen level of the blood, the highest recorded reading being 96.9 mgm. per cent. There was an early and marked increase in the blood creatinine. In 3 patients blood chloride determinations were made and found to be within the normal range. Martland[91] reports a similar normal blood chloride level in 1 patient. Blood sodium and potassium levels were determined in 2 patients by the former investigators[96] and found to be within normal limits.

The disease in the newborn, when it occurs secondary to trauma incidental to birth, is quite different from the fulminating typical syndrome associated with meningococcemia. Goldzieher and Gordon[97] have presented an excellent review of this subject and have emphasized the *hyperpyrexia, tachypnea, cyanosis and convulsions*. Petechiae and skin hemorrhages are only infrequently present and rarely extensive.[93] An abdominal mass is occasionally palpable.

Diagnosis, Prognosis, and Treatment.—The sudden onset, particularly in children, of a fulminating sepsis due to meningococcemia and associated with hyperpyrexia, cyanosis, extensive petechiae and purpura, and vascular collapse should suggest the diagnosis of massive adrenal hemorrhage. This clinical picture becomes especially suggestive if the patient resides where meningitis is prevalent or epidemic.

Until recently the disease has been regarded as uniformly fatal. Within the past several years, however, several apparent instances of recovery have been reported.[98, 99, 100, 101, 102, 103, 104] Since the extent of the hemorrhage into the adrenals may vary considerably, it is entirely conceivable that in some instances the degree of adrenal destruction may be limited enough to permit of subsequent repair provided the patient does not succumb to the sepsis. One must not lose sight of the fact, however, that meningococcemia may occur associated with skin lesions and vascular collapse in which the adrenals show no significant pathology. Recovery from this type of meningococcus sepsis is not uncommon and clinically this condition may easily be confused with the true Waterhouse-Friderichsen syndrome. On the basis of our pathologic experience the adrenal injury is so profound in this latter condition that recovery is most unlikely and the diagnosis in such event is open to grave doubt.

The treatment of the Waterhouse-Friderichsen syndrome is directed to the achievement of three goals: (*a*) combating the sepsis, (*b*) treatment of the vascular collapse, and (*c*) supportive adrenal cortical therapy.

It is questionable as to how significant a role acute adrenal insufficiency actually plays in the syndrome. Generally, *the adrenals are not entirely*

destroyed and there may be considerable areas of relatively normal adrenal cortical and medullary cell In addition the course of events is so rapid and death follows so promptly that true adrenal cortical insufficiency is unlikely to develop within this brief period of time Nevertheless it is wise and desirable to administer large doses of whole adrenal cortical extract intravenously and subcutaneously or cortisone and ACTH preferably the latter two and perhaps fairly large amounts of desoxycorticosterone intramuscularly The procedure to be followed should be that used in the treatment of acute crisis of Addison's disease In addition the vascular collapse should be combated with the usual measures for the treatment of shock such as the use of plasma or whole blood transfusions a continuous intravenous infusion of 5 per cent glucose in isotonic saline and the judicious use of adrenalin Today, because of the marked progress in chemotherapy we are in a much better position to attempt to deal with the septicemia The sepsis in this disease is overwhelming in character and calls for prompt and vigorous treatment with large doses of penicillin and one of the sulfonamides or the other antibiotics Fortunately the meningococcus is responsive to these therapeutic agents and they should be employed simultaneously

Illustrative Cases

The patient was a white male child aged four years who was admitted to the pediatric service of the Mount Sinai Hospital at 2 45 A M and died at 8 A M He had been perfectly well until 5.30 o clock of the previous evening when he began to complain of pains in the right thigh and marked fatigue The temperature at that time was only slightly elevated Three hours later he developed vague diffuse abdominal pain became nauseated vomited and complained of chilly sensations The temperature at this time had risen to 103 F

On admission to the hospital the child appeared stuporous but could be aroused He was intensely cyanotic and tachypneic The cyanosis involved particularly the lips hands lower extremities and lower back There was an extensive purpuric rash involving the skin of almost the entire body The purpuric lesions did not fade on pressure Several petechiæ were noted in the conjunctivæ The ear drums were somewhat congested as was the posterior pharyngeal wall There was no palpable lymphoid adenopathy The lungs were essentially clear except for a few crackles at the bases posteriorly X ray examination of the chest was negative There was some mild tenderness on palpation of the right upper abdominal quadrant There was no nuchal rigidity although the reflexes were sluggish and there was a suggestive bilateral Kernig Peripheral blood studies showed the hemoglobin to be 50 per cent the white blood cell count was 5000 per cmm with 31 per cent polymorphonuclear leukocytes of which only 7 per cent were unsegmented 67 per cent lymphocytes and 2 per cent monocytes A blood culture showed a profuse growth of meningococci (Neisseria intracellularis) A spinal tap revealed clear spinal fluid under normal pressure The spinal fluid count was normal and the culture negative

Several hours after admission to the hospital the child died The total duration of the illness as far as could be determined was approximately fourteen and a half hours At autopsy there was massive bilateral adrenal hemorrhage The brain was normal except for some congestion of the superficial vessels

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Chapter 10

THE TREATMENT OF ADDISON'S DISEASE

Historical — The evolution in the treatment of Addison's disease has been directly related to improvement and advances in biochemical technics It is representative of the painstaking chemical and clinical researches which have resulted in the development of our knowledge concerning the hormones and the endocrine glands that has virtually altered our concept of medicine

After Addison's classical description of the disease almost twenty years elapsed before any substitutive therapy was attempted During this period the patients were treated symptomatically and particularly with "tonics such as iron and arsenic with a uniformly fatal outcome[1] The first effort to treat this disease in a more specific fashion with adrenal extract was made by Stockman in 1867 His results however were entirely unsuccessful From 1867 to 1903 Adams[3] collected a total of 97 cases from the literature in which organotherapy was employed in the form of desiccated whole adrenal and the desiccated extract and aqueous alcoholic and glycerine extracts used either by mouth or by injection Of these 97 cases, 16 patients were reported to have been permanently improved Among these was a patient who responded particularly well to a glycerol extract of fresh sheep adrenal given both by mouth and by hypodermic injection When the use of the extract was discontinued the patient was precipitated into acute adrenal insufficiency which terminated fatally This case was reported by Osler in 1896[4]

In 1895 Oliver and Schafer[5] succeeded in preparing watery alcoholic and glycerine extracts of the adrenal glands which had considerable vasoconstrictor and pressor effects obviously due to epinephrine During the same year these investigators made extracts of the glands of patients with Addison's disease and found them lacking in the pressor substance which they had described as existing in normal glands They therefore concluded that the deficiency of the pressor substance was the cause of Addison's disease

With the isolation and synthesis of pure epinephrine hydrochloride numerous reports appeared on the use of this drug in the treatment of Addison's disease The earliest of these reports was by Raven[6] in 1904 who described remarkable improvement in one case treated with small amounts of this substance Summers[7] reported the use of epinephrine hydrochloride by hypodermic injection and by mouth in a case treated for one hundred forty three days without noticeable improvement at any time In 1920 Dr Muirhead[8] himself afflicted with Addison's disease described the beneficial effects of the use of epinephrine which he took to the point of tolerance by mouth by rectum and hypodermatically

Unfortunately, with the interest attached to the discovery of epinephrine the possibility of the existence of other adrenal hormones was lost sight of until the middle 1920's, when attempts to isolate other potent cortical extracts were again resumed. It had already been learned by that time that epinephrine was of extremely meager value in the treatment of Addison's disease and that it was incapable of maintaining the life of adrenalectomized animals.

In 1927 Rogoff and Stewart[9] succeeded in prolonging the survival period of adrenalectomized dogs with the use of saline extracts of whole adrenal glands. In the same year Hartman and his coworkers[10] described an adrenal extract which prolonged the life of adrenalectomized cats. This extract, in contrast to that of Rogoff and Stewart, contained no epinephrine. In 1929 Pfiffner and Swingle[11] described the successful use of an alcoholic adrenal extract in adrenalectomized dogs. At the same time, Rogoff and Stewart[1] reported the effects obtained by the use of glycerine extracts given both by injection and by mouth to 7 patients with Addison's disease. The results as reported were not particularly brilliant, although some improvement was evident.

The first striking result obtained with the use of cortical extract was described by Hartman and his coworkers[13] in 1930. Dramatic results were obtained in a patient in an acute Addisonian crisis with the use of their extract given subcutaneously and intravenously. In 1931 Rowntree, Greene, Swingle and Pfiffner[14] reported in detail the satisfactory results obtained in patients with Addison's disease who were treated with adrenal extracts prepared according to the method of Pfiffner and Swingle.[11]

With the availability of a potent cortical extract it now became possible to study the underlying electrolyte disturbances in clinical and in experimental adrenal insufficiency, although some observations had already been reported on this point. The characteristic disturbances in blood electrolytes quickly became evident and with it a realization of the value of salt as a therapeutic agent. Soddu[1] demonstrated as early as 1899 that the symptoms of insufficiency in adrenalectomized dogs were somewhat alleviated by saline injections. In 1925 Stewart and Rogoff[16] reported an increase in the survival period of adrenalectomized dogs following the intravenous use of Ringer's solution given with glucose at frequent intervals. Similar results were obtained by several other authors, notably Corey,[17] Banting and Gairns,[18] and Marine and Bauman.[19] The first successful treatment of a patient with Addison's disease with salt given intravenously, by rectum and by mouth was reported by Loeb[20] and confirmed by Harrop and his group.[21] Harrop, Soffer, Nicholson and Strauss[22, 23] succeeded in maintaining adrenalectomized dogs in normal condition over prolonged periods of time without the use of cortical extract but by the administration of salt alone. One dog was maintained in a normal state for a period of five months, at which time the experiment was voluntarily discontinued and the animal promptly precipitated into insufficiency by the withdrawal of salt. In 1936 Wilder, Snell and their coworkers[4] further increased the efficacy of the treatment of Addison's disease by pointing out the importance of and the need for the restriction of the potassium intake in the diet.

By 1935 over three quarters of a century after the original description by Addison the understanding of the underlying phenomena and the treatment of the disease had reached a fairly satisfactory level The outlook of patients with this illness had improved considerably The therapy was not curative, but substitutive in type A good deal, however, was still left to be desired Hypoglycemic episodes occurred over which salt and the cortical extract unfortunately exercised very little effect The pigmentation so characteristic of the disease remained immune to treatment Cortical extract was difficult to obtain and was rather expensive, while the large daily doses of salt required were found burdensome by the patients The first significant advances in the therapy of this illness, however had been made

Between 1936 and 1941 the important contributions to the treatment of Addison's disease consisted in the isolation of various crystalline fractions of the cortical hormones and their preparation synthetically In 1936 and 1937 Mason Myers and Kendall[25] and de Fremery and his coworkers[26] isolated corticosterone and dehydrocorticosterone in crystalline form from the extracts of the adrenal cortex and found that they could maintain adrenalectomized animals in fairly good condition A short while later Steiger and Reichstein[27] announced the synthetic preparation of desoxycorticosterone acetate from stigmasterol and subsequently Reichstein and von Euw[28] succeeded in actually recovering this compound from an extract of the adrenal cortex Levy-Simpson[29] used desoxycorticosterone acetate in the treatment of 2 patients with Addison's disease and found that it exercised an effect qualitatively similar to that of adrenal cortical extract In 1938, Thorn and his group[30] used it in the treatment of bilaterally adrenalectomized dogs and found that it was effective in maintaining these animals in good condition despite a diet low in sodium and chloride Withdrawal of the extract promptly resulted in acute adrenal insufficiency Thorn Howard and Emerson[31] subsequently used this compound successfully in 8 patients with Addison's disease without supplementary treatment with sodium salts or decrease in the potassium content of the diet Ferrebee and his coworkers[32] treated 13 patients with intramuscular injections of desoxycorticosterone acetate and propionate and found that improvement was greater than from any previous therapy However 3 of their patients developed hypertension and 10 patients had edema 3 of whom developed definite cardiac failure Soffer and his group[33, 34] reported results of similar therapy and confirmed the findings of the other authors Emphasis was again placed on the attendant dangers of this therapy the risks of hypertension edema and heart failure

In 1937 Deansley and Parkes[35] reported that the subcutaneous implantation of pellets of estrogens and androgens produced a prolongation of the hormonal effect Utilizing this technic Thorn and his group[36] implanted pellets of desoxycorticosterone acetate subcutaneously in 6 patients with Addison's disease They found that the results obtained with the pellets were similar to those achieved with intramuscular injections except that the former method effected a greater economy in the use of the drug Soffer Engel, and Oppenheimer[33] found that the risks associated with excessive absorption of the desoxycorticosterone acetate from pellets could

be reduced by 'underimplanting' that is implanting fewer pellets than is determined to be necessary by assay and supplementing the therapy with daily small amounts of salt per os

In 1940, Anderson and his coworkers[34] reported the successful use of a preparation of desoxycorticosterone acetate dissolved in propylene glycol and administered sublingually These results were later confirmed by Turnoff and Rowntree [35]

Several other compounds previously discussed in the chapter on the chemistry of the adrenal hormones have been isolated from the adrenal cortex The most significant of these is 17 hydroxy 11-dehydrocorticosterone the so-called Compound E of Kendall or cortisone and Compound F' These compounds and corticosterone and dehydrocorticosterone in contrast to desoxycorticosterone exercise a marked effect on carbohydrate metabolism [39] In the adrenalectomized animal glycogen is stored in the liver and the hypoglycemic episodes prevented Compounds E and F' which have the greatest effect on carbohydrate metabolism enable the adrenalectomized rat to form glucose from lactic pyruvic and certain glycogenic amino acids In contrast to their effect on carbohydrate metabolism these compounds exert less effect on the electrolyte pattern in the adrenalectomized dog Thus Kendall[40] has shown that 0 3 mgm of desoxycorticosterone acetate exercises the same effect on electrolyte excretion as does 2 5 mgm of dehydrocorticosterone and 10 0 mgm of 17 hydroxy 11-dehydrocorticosterone (Compound E) Finally, there is the amorphous fraction of adrenal cortical extract which remains after removal of the crystalline fractions This has a very powerful effect on electrolyte metabolism—considerably more so than desoxycorticosterone acetate

For clinical purposes in the treatment of patients with Addison s disease we have available at present the following therapeutic measures

1 Salt
2 Low potassium diets
3 Whole adrenal cortical extract
4 Desoxycorticosterone acetate
5 Percorten glucoside an aqueous solution of desoxycorticosterone which may be used intravenously
6 Lipo-Adrenal cortex
7 Cortisone and Compound F
8 Various combinations of these therapeutic agents

The Treatment of Patients During Intercritical' Periods —During periods between crisis the occasional patient with Addison s disease may feel quite well without the aid of any particular therapy Except for a rather easy fatiguability, he may be able to attend to his routine functions provided they demand no undue physical or mental efforts But such patients are always teetering on the edge of catastrophy and the most minor circumstances may precipitate them into insufficiency Accordingly it should be understood that every patient with Addison s disease regardless of his state of well being and regardless of the normalcy of the blood electrolyte pattern must always receive treatment The treatment

of choice during intercritical periods is the use of a potent cortical extract or desoxycorticosterone acetate supplemented with an increase in the daily salt intake. Many of these patients can get along extremely well with the aid of salt alone. But although the salt exercises some protective influence, these patients, like the untreated ones, are subject to the hazard of precipitate adrenal insufficiency. Generally speaking, the Addisonian patient even during intercritical periods feels chronically ill and tired, worn out, depressed, and is pretty much incapacitated from any constructive effort. The administration of large quantities of salt will improve his sense of well being, but the administration of extract will improve it considerably more, frequently enable him to return to work, and protect him against the dangers of crisis. Frequently the blood electrolyte pattern can be maintained at normal levels with the aid of salt alone, but just as frequently further aid with extract is required to accomplish this result. The weight of the patient, the blood hematocrit, urea nitrogen and blood sodium level must be used as guides in the amount of treatment suggested. These determinations should be done at frequent intervals, and any downward trends call for a prompt increase in therapy. The presence of any infection however mild, intercurrent gastrointestinal disturbances, or any essential surgical procedure, no matter how minor in character, requires an increase in treatment.

The daily salt content of the average diet is approximately 5.0 to 8.0 grams. Where for one reason or another it is desired to maintain the patient on salt alone, an additional 12 to 15 grams daily is required. This supplementary salt should be administered in the form of capsules or enteric-coated pills taken 4 to 6 times a day. It is never wise simply to urge the patient to salt his food heavily. Such therapy is haphazard and the amount of salt thus consumed is always less than the required quantity. For those patients who encounter difficulties in taking the salt in the form of capsules, the desired amount may be administered dissolved in fruit or tomato juice given at frequent intervals during the course of the day. It should be remembered that excessive quantities of salt may produce edema which can prove very troublesome. It is desirable, therefore, to strike a happy balance, prescribing that amount of salt which will maintain a normal electrolyte pattern and yet not produce nausea, vomiting, diarrhea, or edema. In our experience patients can rarely tolerate more than 12 to 15 grams a day without the onset of some of these unpleasant sequellæ.

Wilder and his coworkers [4] have further enhanced the therapeutic value of salt by pointing out the importance and need for the restriction of the potassium intake in the diet. With a low potassium diet the daily salt requirements are reduced. The normal diet contains approximately 3 to 4 grams of potassium daily. The diets recommended by the Mayo Clinic group contain 1.6 to 1.99 grams of potassium. The usual low potassium diets, however, are not very palatable, and the more elaborate diets suggested by the Mayo Clinic group require preparation that is troublesome for home use. Where supplemental salt is the only therapeutic measure used, a low potassium diet is helpful. With the use of extract, however, its advantages are limited, and as a matter of fact when desoxycorticosterone

acetate is employed there are definite dangers associated with the use of such diets.[41, 42]

Most patients during the intercritical periods require specific hormonal therapy either with or without supplementary salt. Whole adrenal cortical extract was the sole specific therapy until the advent of desoxycorticosterone acetate in 1937. Adrenal cortical extract is used by injection either subcutaneously or intramuscularly. It may be given intravenously, but this route of administration offers no advantage in the absence of acute adrenal insufficiency. The quantity of hormone to be employed is governed by the state of well being of the patient, the blood pressure, weight, appetite and blood electrolyte pattern. Generally speaking 2 to 5 cc. of extract divided into 2 daily injections supplemented with an additional 5 to 8 grams of salt by mouth is adequate to maintain a patient in a satisfactory state provided no undue complications ensue. One need have no fear of giving excessive quantities of extract, since no overdosage symptoms such as are seen with desoxycorticosterone occur. Adrenal cortical extract, however, is expensive and this is one of the factors to be borne in mind in the use of the drug. It is wise to supplement the extract with additional salt by mouth. This not only effects a greater economy in the use of the drug but also provides the maximum protection for the patient. In the presence of any complicating physical disturbance, regardless of whether there are any signs of increased adrenal insufficiency, the quantity of both salt and extract must be increased promptly.

Desoxycorticosterone acetate exercises qualitatively the same effect as does whole adrenal cortical extract but quantity for quantity has considerably greater potency. Desoxycorticosterone is provided in an oily medium (sesame oil) and hence may not be used intravenously. It can be employed by subcutaneous and intramuscular injections, by implantation of pellets and by sublingual administration. The dosage of the drug must be determined carefully since, unlike adrenal cortical extract, unpleasant complications may be induced by overdosage. These will be discussed in detail subsequently, but briefly, too large a dosage can induce hypertension, edema and heart failure, as well as profound muscular weakness and paralysis,[43] the latter two probably the result of an abnormally low serum potassium induced by the hormone. The average Addisonian patient requires 1 to 5 mgm. of desoxycorticosterone given daily by injection in 1 dose. It is wise to supplement this drug too with an additional 2 to 5 grams of salt by mouth. Too rapid a gain in weight, the development of overt edema or the presence of hypertension calls for a reduction in the amount of salt or extract or both. When desoxycorticosterone is employed no restriction in the dietary intake of potassium should be imposed. The dangers of such restrictions have been emphasized by Wilder[44] and Tooke *et al.*[4] Many patients during the intercritical periods get along quite well with injections of this substance given every other day or every third day. In instances of this kind we have found that a satisfactory scheme of therapy consists in reducing the amount of supplementary salt on the day of injection and increasing it during the interim days. Thus on the day of injection the patient receives 2 to 4 grams of salt above that consumed in the diet and on the days between injections 4 to 6 grams. The develop-

ment of upper respiratory infections, gastrointestinal disturbances, *etc* calls for increased amounts of hormone, such as are required under similar circumstances when whole adrenal cortical extract is employed. Recently an aqueous solution of desoxycorticosterone (Percorten Glucoside Ciba) has been made available for intravenous use.

In properly chosen and previously regulated patients the most satisfactory and economical method of treatment is by implantation of pellets of crystalline desoxycorticosterone acetate. The effect of the pellets is identical with that of the injection of the substance in oil. It has the advantages of greater economy and the elimination of the injections which patients find so onerous. However, after the pellets are implanted, control of the patient is *more difficult* and the *development of complications due to excessive* medication requires surgical intervention to reduce the dosage. To avoid this danger, we feel it is wiser to implant less than the required number of pellets and to supplement the treatment with some additional salt by mouth daily. It is important, too, to select the proper kind of patient for implantation. In our experience, patients over forty years of age are poor subjects for implantation. The tendency to develop hypertension and cardiovascular symptoms including angina is pronounced in this group, and the dosage requirement must be readjusted at frequent intervals. Similarly patients who need small amounts of hormone for maintenance and in whom daily injections are not required are adjusted with difficulty with pellets.

In order to obtain satisfactory results by pellet implantation, a prolonged period of observation while on treatment with intramuscular or subcutaneous injections is necessary before this procedure is carried out. During the first few months of treatment with the synthetic hormone, a gradual decrease in the patient's requirement occurs. This is due to the fact that when he is originally seen the patient is usually quite ill and liberal quantities of hormone and salt are required to restore the blood electrolyte pattern to normal and return him to reasonably good health. Much less hormone and salt are required to maintain a well hydrated patient in a normal state physically and chemically than to bring him *to this point* from depleted levels. The result is that there is a progressive decrease in hormonal requirement as the patient's condition improves. If pellets are implanted before the minimal requirement has been achieved, what was an adequate dose at the time of implantation will prove to be excessive several months later. In our therapeutic regimen at present, patients are treated with intramuscular injections for two to three months before implantation is attempted. They receive in addition small quantities of added salt, approximately two to five grams daily. During this period of time they are seen at frequent intervals and the minimal hormonal requirement thus determined. The appearance of hypertension, excessive gain in weight, and fall in hematocrit call for a reduction in the amount of hormone while the reverse with a drop in the level of the serum sodium indicates inadequate therapy. When the satisfactory maintenance dose is established the patient is implanted. The number of pellets to be implanted is calculated as follows. Pellets weighing between 100 and 125 mgm yield approximately 0 3 mgm of hormone daily. The hormonal requirement by pellet is about 60 to 75 per cent of that required by injection. Thus a

patient who requires 5 mgm of desoxycorticosterone acetate by injection daily will require that number of pellets which will release 3 0 mgm daily Since each pellet yields approximately 0 3 mgm implantation of 10 pellets would be required to maintain this patient in a satisfactory state Such implanted pellets can be expected to last for from ten to thirteen months Emphasis should be again placed on the desirability of implanting less than the theoretically required number of pellets This is best done by determining the amount of hormone that the patient requires while receiving 2 to 5 grams of additional salt by mouth In this fashion the supplementary salt intake has reduced the hormonal required Exhaustion of the pellets is readily detectable from the gradual development of signs and symptoms of adrenal insufficiency Re-implantation is simple only a brief period of observation with the equivalent dose of hormone intramuscularly being necessary to demonstrate whether the requirement has changed

The implantation of pellets is of course a surgical procedure, although a very minor one Nevertheless we have found it desirable to fortify our patients with an additional quantity of both salt and extract before the implantation We have encountered no difficulties under these circumstances The pellets are implanted in either infrascapular region posteriorly under local anesthesia Strict asepsis must be maintained A transverse incision 1 to 3 inches in length is made below the inferior spine of the scapula A number of small pockets corresponding to the number of pellets to be implanted 1 to 2 cm in depth is made by blunt dissection in the subcutaneous tissue A pellet is gently dropped into the bottom of each pocket The wound is then closed with fine black silk The pellets must be handled very gently to avoid fragmentation Occasionally pellets will extrude particularly if local infection occurs

As with other forms of therapy the onset of any complicating illness is an indication for additional amounts of salt and supplementary injections of hormone

Both Anderson and his group[37] and Furnoff and Rowntree[38] have reported on the successful use of desoxycorticosterone acetate dissolved in propylene glycol administered sublingually in patients with Addison's disease Our experience[34] which has been very limited to date confirms the effectiveness of the hormone administered through this route However this method of administration has several disadvantages The rationale of the procedure is based on the absorption of the hormone into the blood stream of the highly vascular sublingual area To get an even through the day distribution of the hormone it is therefore desirable to administer it several times a day In our experience at least 3 to 5 times as much hormone is required by the sublingual channel to elicit the same effect as is obtained with a given amount administered by injection This has also been the experience of Thorn Dorrance and Day[44] There is a good deal of wastage of hormone associated with the sublingual route To obtain the maximum absorption it is desirable that the patient retain the material sublingually for at least five minutes Many patients even with training find this difficult and tend to swallow the drug with destruction of its effectiveness The result is that the patient obtains in actuality less than the calculated desirable dose

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Where desoxycorticosterone is used it is employed best in the form of pellets implanted subcutaneously However this method is not the best method for all patients and those to be implanted must be selected judiciously and the dosage requirement adequately determined over a prolonged period of time In general the sense of well being of the patient and his muscular strength are considerably improved if cortisone in a dosage of 10 to 30 mgm daily by mouth is given in addition to the desoxycorticosterone

Symptoms of Overdosage With Desoxycorticosterone Acetate — The dangers associated with the use of desoxycorticosterone are primarily the development of edema hypertension angina and cardiac failure Overdosage was also noted to be associated with other manifestations which are sometimes difficult to distinguish from the prodromal symptoms of crisis Among these are anorexia and marked muscular weakness This phenomenon may be due to the excessive retention of sodium and chloride in the blood and tissues associated with an abnormally low concentration of serum potassium This inversion of the sodium potassium ratio may give rise to the unusual disturbance in neuromuscular function [43,44] This clinical observation has an experimental counterpart in dogs treated with excessive doses of synthetic hormones in conjunction with supplementary salt [46] Relief of the clinical symptoms may be obtained by the administration of potassium It becomes evident that a diet low in potassium may increase the hazard where desoxycorticosterone is used and for this reason such diets should not be employed as supplementary therapy with this drug

The serious symptoms of overdosage with the synthetic hormone are those concerned with the cardiovascular system Alarming hypertension peripheral and pulmonary edema and cardiac failure have been reported with increasing frequency and with several fatalities [3,33,43,46,47]

The hypertension is apparently a specific effect of the desoxycorticosterone Thus it is difficult to produce hypertension with this agent in patients with intact adrenals or in the normal experimental animal and in our experience the ease with which hypertension is induced is directly related to the extent of adrenal cortical destruction It would suggest that in the presence of intact adrenals some compensatory mechanism is set into motion which mitigates the hypertensive effects of the desoxycorticosterone acetate Although the effect of the synthetic material on the blood pressure occurs promptly hypertensive levels are usually not reached until after two to four weeks of constant therapy Alarming elevations of blood pressure can be treated only by reduction in the dosage of hormone administered Reduction of salt intake or treatment with potassium will not affect this symptom If pellets have been implanted and hypertension has ensued one or more pellets must be removed promptly The frequency with which hypertension occurs during treatment is attested to by the fact that in Thorn's series[44] of 64 patients with Addison's disease significant hypertension occurred in 34 per cent

Edema which develops during desoxycorticosterone therapy is due to excessive retention of sodium chloride and water This may become marked enough to produce pulmonary edema and cardiac failure This complication is particularly prone to arise when intravenous saline is used

The added use of 10 to 30 mgms daily of cortisone along with desoxycorticosterone parenterally considerably improves the sense of well being and strength of the patient and reduces the frequency of the complications incidental to the use of desoxycorticosterone.

Summary of Treatment of Patients During the Intercritical Period — Whole adrenal cortical extract and the synthetic hormone desoxycorticosterone acetate are effective therapeutic agents in the treatment of this condition. However, neither represents complete replacement therapy. Both the whole extract and the synthetic hormone exercise a profound effect on the electrolyte balance. Both are capable of causing a retention of sodium and chloride and thus restoring the blood levels of these ions to normal, increasing the urinary excretion of potassium, enhancing the blood volume and improving the hydration of the patient by restoring the depleted fluid reserves. Desoxycorticosterone acetate has a marked effect on blood pressure and if given indiscriminately may produce hypertension. Whole extract exercises some salutory effect on the hypotension indirectly by improving the general condition of the patient but never raises the blood pressure to hypertensive levels. Neither extract affects the pigmentation of Addison's disease. With satisfactory therapy the patient will appear somewhat lighter, but this is the result of improved hydration rather than any specific effect on the pigment metabolism. The synthetic hormone does not effect carbohydrate metabolism[33,34,44] and consequently hypoglycemic episodes may occur with the patient otherwise in excellent condition. Whole adrenal cortical extract, in contrast to the synthetic hormone, has a beneficial effect on the disturbance in carbohydrate metabolism. However, this effect is by no means pronounced and injections of large quantities are required to produce an appreciable result. Nevertheless, hypoglycemia occurs with considerable less frequency in patients being treated with the whole extract than in those treated with the desoxycorticosterone acetate. Continued and prolonged use of the former results in some elevation of the fasting blood sugar level and some improvement in the oral glucose tolerance curve.[33] Where hypoglycemic episodes are a troublesome feature in a patient with Addison's disease, the therapy of choice consists of frequent high protein feedings, the use of adrenal extract or desoxycorticosterone and cortisone (Compound E) or Compound F.

Most patients require treatment with hormone and wherever possible such therapy should be employed since it provides maximum protection for the patient and produces a degree of rehabilitation which cannot be accomplished with salt alone. However, use of hormone should be supplemented with additional salt by mouth. This effects an economy in the amount of hormone used. In deciding whether to employ whole extract or the synthetic product several factors must be borne in mind. Desoxycorticosterone is a much more effective therapeutic agent than is cortical extract and in this sense much more economical, and under ordinary circumstances is the preferable drug. However, symptoms of overdosage can occur with the synthetic hormone. They must be watched for carefully and the dose readjusted accordingly. Patients with repeated hypoglycemic episodes fare better with the whole extract or Compound E or F. In the presence of complicating severe infections or where the need of surgical intervention is imperative, both hormones must be employed.

the nausea and vomiting the elevation of the blood pressure, and the drop in blood nonprotein nitrogen or urea nitrogen

Both whole adrenal cortical extract and desoxycorticosterone should be used in crisis Twenty five to 50 cc of whole adrenal extract is given intravenously at once and at the same time an additional 20 cc subcutaneously and 10 to 20 mgm of desoxycorticosterone intramuscularly During the first twenty four hours the patient continues to receive 5 to 10 cc of the adrenal cortical extract subcutaneously every two to four hours and an additional 10 mgm of desoxycorticosterone is again administered during the course of the day During the first twenty four hours then the patient should receive 100 cc or more of whole adrenal cortical extract and 20 to 30 mgm of desoxycorticosterone During the following days 5 to 10 cc of the whole extract is given 2 to 4 times a day, as well as 5 to 10 mgm of the synthetic hormone twice a day The amount of extract to be used is determined by the clinical state of the patient As the patient s condition is improved there is a gradual tapering off of both the whole adrenal extract and the desoxycorticosterone The ultimate goal is to maintain the patient with intramuscular injections of desoxycorticosterone supplemented with additional salt by mouth

During the period that the patient is receiving intravenous fluids he must be carefully watched for signs of peripheral and pulmonary edema and heart failure At the slightest signs of moisture at the lung bases or the presence of facial or peripheral puffiness the amount of intravenous fluids should be reduced and the desoxycorticosterone entirely eliminated reliance being placed on whole adrenal extract

Blood transfusions are sometimes resorted to in severe adrenal shock but our experiences with this have been unsatisfactory The patients are more easily precipitated into heart failure with transfusion and transfusion reactions are both unpleasant and common in patients with Addison s disease

Epinephrine either in aqueous solution or in oil may be used where the shock is profound

Not all patients with adrenal insufficiency require the elaborate therapeutic regimen outlined above When the patient is in mild crisis intravenous fluids plus considerably smaller quantities of hormone will suffice Where the shock is profound it is well to remember the following

1 Use intravenous fluids freely and over a prolonged period
2 Be extravagant with the amount of whole adrenal cortical extract used
3 Use desoxycorticosterone judiciously and carefully watching for signs of edema and heart failure
4 Never use desoxycorticosterone alone but employ both hormones

In acute adrenal insufficiency as in diabetic acidosis best results are obtained by immediate massive therapy The more prolonged the period of crisis the more irreversible are the changes induced and death may follow despite vigorous therapy It is of paramount importance that the signs and symptoms of crisis be recognized early and treatment instituted

in conjunction with the synthetic hormone The edema subsides rapidly following the withdrawal of the sodium chloride, reduction in dose of hormone, or both

A sudden rapid gain in weight and precipitate fall in the blood hematocrit occurring during treatment indicates the development of edema even in the absence of more overt signs

Circulatory failure can occur in patients treated with desoxycorticosterone because of the hypertension the development of extensive edema and finally as a result of a change in the cardiovascular dynamics induced by the hormone The heart in patients with Addison's disease is small and its musculature flabby During acute adrenal insufficiency there occurs a further decrease in cardiac volume McGavack[49] calculates the cardiac volume in Addisonian patients in crisis to be approximately two-thirds of normal Following treatment with the synthetic hormone there frequently occurs a progressive cardiac enlargement which can become quite marked where the drug is used injudiciously[2, 47, 48, 49] The rapidity with which this occurs suggests that the increased cardiac size is due to dilatation rather than to actual hypertrophy of the muscle fibers With reduction in the dose of hormone and withdrawal of salt the heart will recede in size The enlargement of the heart is due to an additional cardiac burden resulting from an increase in the circulating blood volume and an elevation in blood pressure Electrocardiographic tracings not infrequently show evidence of progressive myocardial damage[44] These findings are much more common in the older patients and it is, of course possible that the physical inactivity and reduced dynamic demands associated with the untreated illness have masked possible underlying cardiovascular disease

When treated patients develop heart failure the therapeutic regimen should include complete bed rest the use of mercurial diuretics digitalization and reduction in dose of hormone and withdrawal of salt The episodes of mild failure will respond well to bed rest and reduction of hormone and withdrawal of salt

The Treatment of Adrenal Crisis — The patient in acute adrenal insufficiency is in shock. The characteristic features of this shock are the dehydration the circulatory collapse and the consequent renal failure Aside from these features which have been initiated by the lack of adrenal hormone there is another much less well defined but equally important factor in acute adrenal insufficiency which is related to the specific effect of the adrenal hormones on cellular metabolism Understanding these aspects of the problem the outline of the treatment becomes clear

It is important to maintain the body heat and the patient should be kept warm with the aid of heated blankets A continuous intravenous drip of normal saline in 5 per cent glucose is immediately started During the first twenty four hours between 3000 and 4000 cc of fluid should thus be administered This represents about 30 to 45 drops per minute The intravenous fluids should be continued until the patient is definitely out of shock and capable of taking adequate fluids and salt by mouth After the first twenty four hours the amount of fluids administered intravenously is determined by the clinical status of the patient The most satisfactory guides are the subsidence of the gastrointestinal symptoms particularly

unfortunate complications is small The enormity of the hazards under these circumstances must be considered before surgery is decided upon

When surgery is unavoidable the preoperative preparation and the choice of anesthetic are of great importance If adequate time is available at least forty-eight hours should be employed for preparation During this period the patient is given 30 cc of whole adrenal cortical extract subcutaneously daily in divided doses and *20 to 30 mgm of cortisone* as well as 10 mgm of desoxycorticosterone intramuscularly the latter in 1 dose each day This dosage is continued throughout the operative day and for one or more days until the patient is well beyond the danger of developing acute adrenal insufficiency On the morning of operation a constant intravenous drip of isotonic saline in 5 per cent glucose is started and continued for a twenty four hour period or longer if necessary During the operative day in addition to the extract given as described above 25 cc of whole adrenal cortical extract is administered intravenously just before the operation and again during or after the operative procedure if there is a precipitate fall in blood pressure or if the patient shows even mild signs of shock In addition epinephrine may be employed subcutaneously to aid in combating shock Vigorous therapy must be continued until the patient is well on the road to recovery The patient must be watched carefully for the development of peripheral or pulmonary edema or signs of heart failure If these begin to manifest themselves then the intravenous fluids and the synthetic hormone must be discontinued and the dose of whole adrenal cortical extract increased

The above outline of treatment is based on the assumption that there is adequate time for preparation and that the patient is in good condition When the situation is such that the patient is in mild or severe insufficiency then a longer period of time must be employed for preparation with the use of more fluid salt and larger doses of hormone No patient is ready for operation unless the blood pressure blood electrolytes hematocrit and urea nitrogen are at normal levels Where the surgical situation is acute and immediate intervention indicated it is wiser to accept the risk of postponing the operation for at least twenty four hours for purposes of preparation than to subject the unprepared patient to surgery

Whenever possible local anesthesia should be employed When general anesthesia is essential the patient should be kept under as lightly as possible consistent with the rapid and successful execution of the surgical procedure At present the general anesthetic of choice is a combination of gas oxygen and ether Spinal anesthesia and avertin should be avoided Preoperative and postoperative morphine should be administered in minimal doses

It is well to emphasize again that no patient with Addison s disease is a good surgical risk All operative procedures however minor should be avoided if possible Where major procedures are involved the mortality rate will be high despite the most thorough preoperative preparation These factors must be borne in mind in evaluating the need for surgical intervention

Treatment of Addison s Disease During Pregnancy —Pregnancy is strongly contraindicated in the presence of Addison s disease but we are

promptly There are two additional hazards that it is well to bear in mind The patient in crisis may, in addition develop hypoglycemia or the latter may precipitate the crisis This is best controlled by the intravenous solution of glucose in saline and by the use of large doses of whole adrenal cortical extract and cortisone or Compound F Finally, in acute adrenal insufficiency the patient should be spared as much trauma and effort as possible These patients are in a critical condition and it is indeed amazing what slight effort or minute trauma may result in a fatal outcome

The Treatment of Acute Infections in Addison s Disease —Patients with Addison s disease are notoriously susceptible to intercurrent infections and particularly acute upper respiratory infections The prompt and proper treatment of these complications is important since they play a very prominent role in precipitating patients into crisis The presence of infection increases the salt and hormone requirements and if this is borne in mind and additions to therapy instituted at the first signs of the complicating disease episodes of crisis can be avoided Patients with Addison s disease tolerate the antibiotics extraordinarily well and when the indications for the use of these drugs are definite they should be used in full doses

The presence of any infection is of serious import in Addison s disease not only because of the danger of crisis but also because the infection itself however mild and apparently innocuous its original character is less readily controlled spontaneously and tends to assume serious proportions The patients must therefore be fortified by increasing the dose of hormone and salt In the presence of this complication even in the absence of acute adrenal insufficiency both the whole adrenal cortical extract and desoxycorticosterone acetate should be administered If crisis is present the patient is to be treated as previously outlined plus the oral or intravenous use of full doses of sulfonamides or penicillin aureomycin terramycin streptomycin or chloromycetin if these are indicated [50 51] The most common intercurrent infections in Addison s disease are those due to the hemolytic streptococcus and pneumococci both fortunately very responsive to the antibiotics

The Treatment of Surgical Complications in Addison s Disease —Before the advent of specific hormonal therapy the patients with Addison s disease were notoriously poor surgical risks Any surgical procedure however mild was fraught with the ever present danger of the development of crisis or of sudden death Procedures of as minor a character as simple dental extractions could and usually would precipitate patients into acute adrenal insufficiency while the more serious surgical procedures usually terminated fatally Today with our tremendous advances in therapy the hazards are considerably reduced but the dangers are still very great and no patient with Addison s disease should be subjected to a major operative procedure unless there is no alternative The decision to intervene surgically should be arrived at only after the most careful consideration with due awareness of the perils involved The dangers are particularly great in the presence of acute intraabdominal emergencies associated with infections such as acute suppurative appendicitis and empyema of the gall bladder Despite the best preoperative preparation at present available, the chance of survival of the patient with Addison s disease with these

reported 2 cases of Addison's disease in which adrenal transplantations were attempted. Healthy cortical tissue was obtained following nephrectomy in 2 patients and promptly transplanted. In neither instance were the donor and the recipient of identical blood groups. The cortex was washed in saline and within an hour under local anesthesia the cortex having been cut up in small pieces about the size of match heads, the transplants were introduced into avascular pockets in the rectus muscle and the pockets were closed with a single stitch of fine catgut. The first patient was transplanted with 24 pieces of cortical tissue and the second patient with 64. The first case died fourteen days after transplantation of a progressive infection starting in a bed sore. Microscopic study of the transplants showed that they were in part viable. The second case, according to the authors, showed definite improvement, although the patient was apparently lost sight of six months after the transplantation. In the second case the transplants were only partially competent at best, since there occurred no lessening of pigmentation or increase in blood pressure (which remained at the low level of 80/48) and following a moderately low salt diet there occurred a marked drop in blood sodium and beginning signs of acute adrenal insufficiency.

Three of our patients with Addison's disease have been subjected to adrenal cortical transplantation with a complete lack of success. In October 1946 Broster and Gardiner Hill reported 1 patient in whom a successful take was obtained. The donor was a young woman with virilism. The adrenal was removed intact, its veins being cut long so as to leave about 1 inch attached to the gland. The vein was perfused with heparin solution and the graft placed in normal saline in a sterile glass container. This was then put into a second sterile glass container and transferred to a vacuum flask at body heat. The recipient was prepared as follows. An incision was made along the outer border of the left rectus muscle, the rectus retracted inwards and 1 inch of the deep epigastric artery and vein was exposed and cut medially. Arterial bleeding was controlled by finger pressure, and the wound was bathed in heparin solution. The artery and vein were each caught up laterally by a stitch of the finest catgut threaded on two straight needles. By this time bleeding had ceased. The artery and then the vein were separately piloted into the adrenal vein by pushing the two needles up the latter and causing them to emerge at separate points on the surface of the gland. The vessels were anchored in position by tying the stitch across the intervening cortex. To prevent any backflow of blood a stitch was tied across the open end of the adrenal vein, dividing the epigastric artery and vein into two separate compartments. The graft lay snugly in the extraperitoneal fat when placed behind the rectus muscle.

Postoperatively and for thirteen months thereafter the patient was given oral supplementary salt therapy but received no cortical extract. During this period of time her pigmentation lessened markedly, while the blood pressure returned to normal levels and at times even attained hypertensive levels. Three salt deprivation tests performed during this period were entirely normal. Subjectively the patient felt well.

In a recent personal communication from Dr. Broster he describes the patient as being cured of Addison's disease two and one-half years after

in agreement with Thorn[44] that when pregnancy is established it is safer to attempt to carry it to termination than to interrupt it

The metabolic changes which occur in Addison's disease during gestation are helpful.[6] Rogoff and Stewart[5] and Swingle and his group[53] have demonstrated that the hormonal requirement of the adrenalectomized animal is greatly reduced during pregnancy. This is probably due to several factors: 1) The fact that progesterone and the estrogenic hormone have some sodium retaining effect and thus exercise a beneficial influence on the maintenance of life of the adrenalectomized animal,[53, 55] and 2) The secretion of the fetal adrenals or perhaps the placenta provides at least in part replacement of necessary adrenal cortical hormones. During pregnancy in Addison's disease there occurs a spontaneous increase in the urinary excretion of both the neutral 17 ketosteroids and the 11-oxygenated steroids.[64]

The first trimester of pregnancy and the period during and immediately following delivery offer the greatest hazards to the patient. During the early weeks of gestation the persistent nausea and frequent vomiting will predispose the patient to adrenal insufficiency. The patient with Addison's disease is even more prone to these physiologic complications than is the normal individual and during this period desoxycorticosterone therapy should be supplemented with whole adrenal cortical extract and the salt intake increased. If nausea and vomiting persist intravenous saline and glucose should be administered at frequent intervals. The blood pressure, hematocrit and blood sodium should be maintained at normal levels and their determinations checked repeatedly. During the middle and last trimester of pregnancy there is a considerable increase in the circulating sex hormones and secretion from the fetal adrenals and placenta. During this period the dosage of desoxycorticosterone and salt must be readjusted since edema and hypertension are likely to ensue.

The delivery and the postpartum period present the greatest dangers. The severe physical efforts during delivery and immediately following delivery, the blood loss, precipitate removal of adrenal hormones provided by the placenta and adrenals of the fetus, and the sudden drop in titer of the sex hormones may readily induce acute adrenal insufficiency. Therefore immediately prior to delivery the patient must be treated for impending crisis. Large doses of whole adrenal cortical hormone should be given intravenously and subcutaneously, the dose of intramuscular desoxycorticosterone increased, and intravenous fluids promptly started and continued throughout delivery and during the postpartum period until the danger of crisis has been eliminated.

The Treatment of Addison's Disease With Transplantation of Adrenal Tissue.—Theoretically the ideal treatment of Addison's disease would be the successful transplantation of adrenal tissue. This would represent complete replacement therapy of a permanent character. Many attempts at transplantation of adrenal tissue have been made in Addison's disease. None was completely and very few were even partially successful. Jaffe[56] succeeded in establishing successful adrenal cortical transplants in 4 out of 15 rats. Homotransplants were used. D'Abreu[57] collected from the literature the cases of adrenal cortical transplantations in Addison's disease and reports 1 possibly successful instance. Beer and Oppenheimer[9]

1 The coexistence of active tuberculosis elsewhere in the body If the disease is associated with active and progressive tuberculosis the outlook is essentially poor since we are then dealing with two serious clinical entities—the generalized tuberculosis and the suprarenal disease And even though the suprarenal insufficiency may be controlled with adequate hormone therapy, the patient will succumb to the tuberculous process elsewhere This is particularly true in the presence of miliary renal meningeal, and advanced pulmonary lesions Where the tuberculous process is quiescent or stationary the outlook is *no worse* than in the case of simple adrenal cortical atrophy

2 The nature of the destructive process in the adrenals Patients with adrenal cortical atrophy are more responsive to specific therapy than are those with tuberculous processes in the adrenals The patients with atrophy present no additional generalized problems to contend with Unlike the patients with tuberculosis their health has not been previously undermined by a prolonged and devastating illness with profound cachexia

3 The sequence of onset of symptoms The prognosis is good where the only signs present are pigmentation and hypotension The presence of these signs alone indicates relatively little involvement of the adrenal cortex and many years may elapse before the patient develops incapacitating or critical symptoms Those instances in the literature in which patients have lived for ten years or more without treatment are instances in which patients have had only pigmentation and hypotension for ten years or more The onset of severe asthenia weight loss nausea vomiting and diarrhea indicates extensive involvement of the adrenal cortex and with the advent of these symptoms the prognosis promptly becomes ominous Where the gastrointestinal symptoms the asthenia and weight loss manifest themselves before or directly after the appearance of the pigmentation the outlook is extremely poor and without proper therapy the disease will pursue its usually fatal course

4 The degree of disturbance of carbohydrate metabolism The presence of frequent hypoglycemic episodes subjects the patients to considerable danger Hypoglycemic shock in patients with Addison's disease may be very severe and life threatening and always needs prompt therapy since the tendency to spontaneous relief is lacking

5 Finally the nature of the therapy employed The sense of well being and the life span have been considerably increased with the use of salt adrenal cortical extract and desoxycorticosterone However it must be remembered that as yet none of these drugs represents complete replacement therapy In the days before specific hormone treatment most patients with Addison's disease were invalids throughout the course of their illness and generally incapable of any constructive effort In Thorn's series[44] of 64 patients 50 per cent were fully rehabilitated during treatment with desoxycorticosterone acetate and 25 per cent were greatly improved although not completely restored to normal health and activity This author's statistics on the mortality are very illuminating Prior to 1930 when there was no specific therapy approximately 63 per cent died at the end of 1 5 years During the years 1930 to 1937 when salt and whole adrenal cortical extract was the treatment of choice of 34 cases 43 per cent

the operation In addition two other patients were operated upon one of whom died during the anesthesia while the other was successfully transplanted It should be remembered that the operative procedure involved subjects the Addison patient to a very considerable risk It is imperative that they be prepared properly as for any other surgical procedure

With the exception of the report cited above the results to date of adrenal transplantation in general have been unsatisfactory but the method is so completely rational and its potentialities for success so good that it is to be hoped that studies will be continued in an effort to establish the proper conditions and media for successful transplantation

Sensitivity of Patients with Addison's Disease to Various Drugs —As a general principle it should be recognized that these patients are unusually sensitive to many drugs and dangerously so to some The general dosage schedule which applies to normal individuals must be reduced when applied to the Addisonian patients They are unusually sensitive to narcotic agents like morphine and codeine and to sedative drugs like paraldehyde the bromides and the barbiturates These drugs must be employed cautiously and in small doses when indicated Coma and respiratory failure can follow upon the use of amounts which may ordinarily be employed with impunity This is particularly a problem in the presence of acute infections with high fever when the Addisonian patients tend to become markedly restless and frequently disoriented and sedation is indicated The patient with Addison's disease is dangerously sensitive to insulin and to a somewhat lesser extent to thyroid extract and thyroxine These drugs may precipitate episodes of acute adrenal insufficiency Thyroid extract should be employed in small doses only in the presence of a very low basal metabolic rate and when the clinical symptoms of hypothyroidism are definite Many patients with Addison's disease have some reduction in the basal metabolic rate This is usually not associated with symptoms which are amenable to thyroid therapy

In contrast to the drugs just mentioned the Addisonian patient tolerates epinephrine and the sulfonamides very well When the latter are indicated in the presence of infection they should be used vigorously either by mouth or by intravenous administration in the dosage ordinarily employed in patients without Addison's disease Penicillin aureomycin terramycin chloromycetin and streptomycin may be employed with complete safety

Prognosis in Addison's Disease —The prognosis in Addison's disease is very different today from what it was prior to the advent of specific hormone therapy [61] Guttman [59] in an analysis of 566 cases collected from the literature before 1930 found that the average duration of life where cortical atrophy was present was 4 4 months and for tuberculosis 2 5 months although he also reported instances where the disease existed for more than ten years This form of statistical analysis is somewhat deceptive since it deals with information only indirectly obtained and from authors whose criteria for diagnosis and date of onset differ It is the general impression[60] that without specific therapy the duration of life from the onset of symptoms averaged one to two years patients with atrophy of the adrenal cortex offering a slightly better prognosis than those with tuberculosis In general the prognosis depends upon the following factors

and darkening of the skin Upon investigation the blood pressure was found to be 60 40 She had typical Addisonian pigmentation and abdominal roentgen ray studies revealed extensive calcification in the regions of both adrenal glands The blood sodium at the time of admission was 123 4 and the chlorides 94 meq l The urea nitrogen was 21 mgm per cent The patient was markedly dehydrated and in obvious Addisonian crisis Treatment was started at once with a continuous intravenous drip of isotonic saline injections of desoxycorticosterone acetate intramuscularly and the administration of salt by mouth There followed a prompt remission of the symptoms with a return of the blood sodium and chloride concentration to normal levels and an increase in the blood pressure to 110/70 She was then maintained with daily intramuscular injections of 1 mgm of desoxycorticosterone acetate plus 6 grams of supplementary salt by mouth On this regimen she felt well and the blood pressure weight and blood sodium concentration were maintained within normal limits

She continued to do well for a period of approximately a year One week before the second admission to the hospital the patient noted slight puffiness of the face and edema of the ankles and her family physician found her blood pressure to be 140 90 She complained of weakness anorexia and some nausea On admission to the hospital a week after the onset of these symptoms the patient appeared acutely ill She complained of marked weakness and nausea although no vomiting had ensued There was moderate edema of the face and eyelids and the blood pressure was 150/90 the blood sodium was 116 and the chlorides 78 meq/l The urea nitrogen was 10 mgm per cent while the serum proteins were 6 3 grams per cent The hematocrit was 30 the hemoglobin was 77 per cent and the white blood cell count was 4 800 with a normal differential The examination of the urine was negative At this time no evidence of pharyngitis or tonsillitis was observed Four hours after admission to the hospital the patient began to vomit and the blood pressure fell to 110 70 It was now obvious that she was in severe adrenal insufficiency despite the presence of edema a low hematocrit and a normal or slightly elevated blood pressure In view of these phenomena it was felt advisable to change from desoxycorticosterone acetate to adrenal cortical extract Accordingly she was given 20 cc of whole extract intravenously and 10 cc twice a day subcutaneously In addition a constant intravenous infusion of 5 per cent glucose in isotonic saline was administered The following morning there was a consideralbe clinical improvement and the blood pressure varied between 125/84 and 100/70 The same regimen was continued and thirty six hours later after the intensive therapy was instituted she felt quite well The blood sodium was now 126.8 meq/l and the chlorides 95 meq/l Although the blood sodium had not yet attained a normal level it was considerably higher than it had been previously It is interesting to note that despite the administration of 2800 cc of fluids intravenously the edema had entirely subsided

Two days after the hospital admission the patient's temperature rose suddenly to 103 F and the next day to 105 4 F Examination at this time revealed a markedly injected and edematous pharynx with startling swelling of the tonsils Hemolytic streptococci in large numbers were cultured from the throat Concomitant with the febrile reaction there occurred a drop in the blood pressure to 95/60 and a pronounced fall in the blood sodium to 116 meq l The adrenal cortical extract was increased to 50 cc a day of which 30 cc a well as an initial dose of 4 grams of sodium sulfadiazine followed by 1 gram every four hours was administered intravenously In addition the constant intravenous infusion of 5 per cent glucose in isotonic saline was continued During the next two days the patient appeared desperately ill The temperature remained at 105 F and she was completely disoriented On the morning of the third day the temperature fell precipitately to 100 F and from this point on recovery was fairly rapid When recovery was well advanced the intravenous medication and fluids were discontinued and the amount of adrenal cortical extract given subcutaneously was gradually reduced to 4 cc

died at the end of 1.5 years. With the introduction of desoxycorticosterone acetate, 14 per cent of 158 cases died at the end of 1.5 years. The actual results of treatment with whole adrenal cortical extract are better than those quoted above, since the period 1930 to 1937 included the early days of adrenal cortical hormones when it was available in only limited quantities and was of variable and usually limited potency.

PROGRESS IN THERAPY

Year	Therapy	No. of patients treated	No. of patients living	Duration of life[1]	
				Range	Average
1924–31	Adrenalin	6	0	1–20 days	8 days
1932	Cortical Extract	2	0	4½–13 weeks	8½ weeks
1932–34	Cortical Extract and Sodium Salts	4	0	2–14 months	6 months
1935–39	Potent Cortical Extract and Sodium Salts	8	0	2 months to 5½ years	1.6 years
1939–48	Desoxycorticosterone, Sodium Chloride, Cortical Extract	22	13	1 month to 9 years	3.6 years

[1] Calculated from the date of the first hospital admission when the diagnosis was established and therapy instituted.

We approached the statistical problem in relation to the effect of therapy on the length of life in a somewhat different fashion. An analysis of our data as outlined in the table indicates that the duration of life from the time of the first admission to the hospital has increased very considerably with present day methods, in contrast to the results previously obtained. The patients were usually admitted to the hospital in acute crisis and from 1924 to 1930 or 1931, when therapy consisted of the use of adrenalin alone, the majority of patients died within eight days. In 1932, when cortical extract of a low potency in conjunction with the use of salt came into general use, survival after this initial period of crisis was considerably lengthened. This prolongation period was further markedly increased with the advent of a potent cortical extract and the use of desoxycorticosterone acetate. Of our group of 30 patients who were treated with potent cortical extract or with the synthetic desoxycorticosterone acetate, 13 are still alive, 10 of whom have so far survived from four to thirteen years after the institution of treatment. Eight of these 10 patients are capable of indulging in the usual community activities and of providing for themselves financially. This is a far cry from the almost hopeless results originally obtained, but still leaves a good deal to be desired. As more fractions of the adrenal cortex are isolated and identified, and hence a more complete replacement therapy becomes possible, it is reasonable to expect a further increase in the survival period and rehabilitation of these patients.

Illustrative Cases

CASE 1.—S. K., the patient, is a fifty-nine-year-old white Russian housewife who was admitted to the hospital in June, 1941, for study. She complained of marked weakness, loss of 25 pounds in weight, anorexia, nausea and vomiting

millimol per liter The hormone was now reduced to 1.5 mgm with 5 grams of salt daily Six days later, there was no change in the weight or blood pressure and the blood chemical constituents remained perfectly normal Clinically the patient felt very well In January 1940 3 pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously in the left infrascapular region The average weight of each pellet was 110 mgm and it was calculated that the patient would absorb approximately 0.9 milligrams of the drug daily In addition he received 5 grams of salt by mouth During the first six months after the implantation he did not show any further subjective improvement and although he felt quite well he did not feel strong enough to return to work or to lead an entirely normally active life His weight fluctuated between 136 and 142 pounds (62 to 64 kg) his blood pressure was approximately 115/80, and the blood electrolytes remained normal However starting the seventh month gradual and progressive subjective improvement became apparent and was manifested by his indulging in normal activities including considerable exercise such as wood chopping About one year after implantation he was readmitted because of the recurrence of weakness anorexia and weight loss during the previous weeks On admission his weight was now 121 pounds (55 kg) The hematocrit had risen to 46 per cent the blood sodium and chlorides had fallen to 135.0 and 100.0 milliequivalents per liter respectively The blood pressure was 104/60 When the added daily salt was discontinued for four days his weight fell further to 118 pounds (53.7 kg) the hematocrit rose to 49.8 per cent the blood pressure fell to 88/58 and the blood sodium and chlorides were now 129.0 and 96.0 milliequivalents per liter The urea nitrogen was 22 mgm per cent The patient felt very weak and it was necessary to administer intravenous saline After restabilizing the patient on the parenteral hormone for several days he was implanted with 3 pellets and discharged shortly thereafter in excellent condition taking 5 grams of added salt a day The blood sodium on discharge was 144.0 milliequivalents per liter Since discharge he has led an entirely normal life returned to work and has had no manifestations of either insufficiency or overdosage His blood pressure averages about 110/80

Comment —This patient has been under treatment for Addison s disease in our hospital for twelve years During most of this time his condition has been excellent and he has been able to return to work He has weathered a number of minor upper respiratory infections without difficulty In treatment we attempted to avoid the development of the complications so frequently seen following zealous treatment with the synthetic hormone For this reason he was deliberately underimplanted and the therapy supplemented with the aid of a small amount of oral salt daily On this regimen he did quite well It should be noted again that exhaustion of pellets was manifested by gradual signs of progressive adrenal insufficiency extending over a period of several weeks In no cases of implantation under our observation have we seen any instances of precipitate development of acute adrenal insufficiency without previous warning symptoms indicating exhaustion of the pellets

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per day In addition, she now received 8 grams of supplementary salt orally daily The sulfadiazine in doses of 1 gram every four hours was continued for three days after the temperature returned to normal levels Ten days after admission the patient was perfectly well The blood sodium and chlorides were 132 9 and 102 meq/l respectively and the blood pressure was 120 80

Comment —Prior to the advent of adequate therapy the development of such severe acute infections frequently proved to be the unfortunate nemesis of patients with Addison's disease The problems that had to be contended with were due to the tendency of even mild infections to spread the relative inability to control them and finally the fact that the patient was usually precipitated into severe crisis The recovery of the patient just described may be attributed justly to vigorous therapy with specific hormones and intravenous fluids to control the adrenal insufficiency and to the use of sulfonamides to control the infection In the presence of infections cortical extract must be used in large doses and when the sulfonamides penicillin aureomycin streptomycin and chloromycetin are indicated they *should be employed freely and in doses with which any* normal patient with a severe infection is treated

The effects of the desoxycorticosterone acetate on this patient were interesting The amount of synthetic hormone that she received was not enough to maintain the blood electrolytes at normal levels or to prevent the development of adrenal insufficiency but the blood pressure was maintained at normal and at times even reached mild hypertensive levels The dissociation of electrolyte and hypertensive effects mentioned elsewhere in this chapter of the synthetic hormone are so clearly demonstrated in this case The results emphasize the specificity of the effect of the desoxycorticosterone *acetate on the blood pressure in the presence of disease* of the adrenal cortex

CASE 2 —I C a man aged thirty four years was admitted to the hospital on November 20 1939 with a characteristic clinical picture of Addison's disease His weight was 129 pounds (58 5 kg) the blood pressure was 94/66 the hematocrit was 47 per cent the blood sodium was 127 and the chlorides 100 milliequivalents per liter The blood urea nitrogen was 21 and the sugar 95 mgm per cent The CO_2 content was 26 5 millimols per liter From November 20 until November 30 he was treated with 15 grams of supplementary salt by mouth At the end of this ten day period he lost 2 pounds (0 9 kg) in weight and there was no change in the blood electrolytes blood pressure or hematocrit reading He continued to complain of nausea and profound asthenia and the intensity of the pigmentation increased On November 30 daily intramuscular injections of 5 mgm of desoxycorticosterone acetate were started in addition to the 15 grams of salt There occurred an immediate improvement in clinical symptoms and by December 11 he felt well enough to get out of bed The nausea and anorexia had entirely disappeared and he felt considerably stronger His weight at this time was 132 pounds (60 kg) the blood pressure was 102/68 and the hematocrit level had fallen to 39 per cent The blood electrolyte pattern returned to normal the blood sodium being 140 6 and the chlorides 107 meq l The blood urea nitrogen was 6, and the sugar 60 mgm per cent while the CO content was 28 1 millimols per liter On December 19 the dose of desoxycorticosterone acetate was reduced to 2 5 mgm daily while the supplementary salt intake had been decreased to 5 0 grams daily Eight days later with this regimen his weight had increased to 136½ pounds (62 kg) and the blood pressure and hematocrit level remained constant at 106/64 and 38 per cent respectively The blood sodium was 143 9 and the chlorides 109 milliequivalents per liter The urea nitrogen was 12 and the sugar 75 mgm per cent and the CO_2 content was 25 8

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It is important to emphasize once more the protean character of the manifestations With the sexual abnormalities there may or may not be present the additional metabolic disturbances such as obesity, hypertension and so on Or these metabolic disturbances may be the predominant part of the picture with relatively lesser alteration in the other manifestations This latter statement is particularly true when the disease develops in adult males

In a general way, we can say that the disease has been associated with the following pathologic abnormalities

1 Tumors of the adrenal cortex
2 Hyperplasia of the adrenal cortex
3 Basophil adenomata of the anterior lobe of the pituitary
4 Sarcomatous and undifferentiated tumors of the anterior lobe of the pituitary
5 Arrhenoblastoma of the ovaries
6 Adrenal cortical rest tumors of the ovaries
7 Granulosa cell tumors of the ovaries
8 Multiple corpus luteum cysts and diffuse luteinization of the ovaries
9 Morgagni Morel syndrome (osteitis frontalis interna)
10 Tumors of the pineal body, or more properly disease of the hypothalamus
11 Tumors of the thymus

The cause and effect relationship between the observed pathology and the full blown clinical picture of the disease is by no means entirely clear It is astonishing that such a large number of different pathologic findings can produce the identical clinical picture It is reasonable to suppose that there is in all probability one common denominator which determines the clinical symptoms

In this chapter we shall concern ourselves essentially with the picture produced by the diseases of the adrenal and by the basophilic cell alterations of the pituitary since these two seem to be so closely related The other causative factors will be considered as problems in differential diagnosis

Historic Considerations — The dramatic character of this disease is such that its occurrence attracted attention and note even in the days of antiquity Pliny[1] described the unusual growth and attainment of maturity of a male child at the age of three Craterus quoted by White described a male subject whose progress from infancy to senility occurred within a span of seven years This case is further embellished to include marriage with offspring during this short span Unquestionably the clinical manifestations of many of these cases were grossly exaggerated The striking nature of the disease lent wings to the imagination But there are enough consistent observations in these descriptions as a whole to render the disease recognizable today as instances of the adrenogenital syndrome

Chapter 11

ADRENOGENITAL SYNDROME

VIRILISM, CUSHING'S SYNDROME, ADRENAL CORTICAL HYPERPLASIA AND ADRENAL CORTICAL TUMORS

Introduction — There has been a good deal of confusion concerning the etiology and even the symptomatology of these diseases classified under the headings of virilism, adrenogenital syndrome, Cushing's syndrome. The reasons for the confusion reside in part in the apparently large number of etiologic factors with which the clinical picture has been associated, and in part because of the variety of clinical manifestations that the disease, or perhaps diseases, has assumed. The clinical picture is influenced considerably both by the age and sex of the patient and by the underlying hormonal disturbances and to a much lesser extent by the nature of the pathology. That this last factor is relatively slight is shown by the fact that the determination of the cause of the symptoms frequently represents a difficult problem in the differential diagnosis. With an increase in our knowledge of the biochemistry of the endocrines within recent years there has occurred some clarification and at the same time some increase in confusion in the unraveling of our particular problem. We now know more than our medical forebears did but not enough and certainly not enough at present to offer definite criteria and conclusions concerning these problems.

For purposes of clarity it is desirable to divide the symptoms into three large groups:

1. Those associated with premature sexual and physical development.
2. Those associated with signs and manifestations of virility.
3. Finally metabolic abnormalities which are part of the disease but are not manifestations of disturbances in sexual physiology.

In the first group belong the signs and symptoms of pseudohermaphroditism and precocious physical development. In the second group are the the signs of precocious sexual development, the manifestations of male virilism in the female (such as hirsutism, enlargement of the clitoris, *etc*) and in the male signs of feminization. In the third group occur the development of obesity, hypertension, glycosuria, osteoporosis, *etc*. The symptoms of the first two groups are referred to as the adrenogenital syndrome. The third group is classed as Cushing's syndrome.

When the disease develops during the intrauterine period pseudohermaphroditism will result. The onset of the disease before puberty is associated with precocious physical and sexual development. After puberty in the female signs of virilism will become striking, while in corresponding males some signs of feminization and impotence will be evident.

glycosuria The hirsutism dated back to the age of nineteen At autopsy the adrenal cortices were found to be hyperplastic In 1926 Parkes Weber[10] described a case of virilism associated with cutaneous striæ purpura hypertension amenorrhea and obesity Some years later Hunter and his coworkers[11] reported a similar case which showed in addition a marked decrease in glucose tolerance and extensive decalcification of the lower spine At autopsy the case reported by Parkes Weber showed a minute basophil adenoma of the anterior lobe of the pituitary Hunter's patient had a malignant tumor of the vaginal wall which had apparently arisen from an adrenal rest In this general way one sees the gradual unfolding of the combination of the adrenogenital syndrome with those additional metabolic disturbances subsequently characterized as Cushing's syndrome

The Relation of Cushing's Syndrome to Basophil Adenomas of the Pituitary and to Adrenal Cortical Tumors and Hyperplasia —In 1932 Cushing[1] called attention to the fact that those metabolic disturbances such as osteoporosis glycosuria hypertension and painful obesity *etc* which sometimes occur in association with evidences of virilism are frequently associated with the presence of a basophilic adenoma of the anterior pituitary He collected 12 cases from the literature of this mixed syndrome in 8 of which there were careful autopsy studies Two of these cases had basophilic adenoma as the only abnormal pathologic finding One case had a pituitary adenoma of the anterior lobe made up of undifferentiated cells and another case of a similar tumor plus an adrenal cortical adenoma One patient showed a possible adenomatous like structure in a fibrosed area of the anterior pituitary Another patient showed only adrenal cortical hyperplasia Finally 1 case presented no evidence of any changes in either the pituitary or adrenals

Cushing's conception of pituitary basophilism as a cause of the syndrome under discussion aroused a good deal of comment and considerable criticism The fact that the syndrome could and did occur in patients who showed no basophilic tumors or hyperplasia and its occurrence under a fairly large variety of other pathologic circumstances occasioned a good deal of skepticism concerning the clinical significance of the basophilic adenomas The major contention centered around the relative importance of these adenomas in contrast to the adrenal cortical tumors and hyperplasia The relatively frequent association of the basophil tumors with adrenal cortical hyperplasia raised the perpetual question as to which came first Cushing[1] commented—"And if the acidophilic adenomas of acromegaly inevitably cause hyperplasia not infrequently associated with actual adenomata of the adrenal cortex it is reasonable to assume that basophilic adenomas may well enough do the same" Moehlig and Bates[12] suggested that the primary change occurred in the adrenals while the alterations in the basophilic elements in the pituitary were secondary They reported a case in which at postmortem examination a large malignant tumor of the kidney probably adrenal in origin was found The pituitary of this patient showed marked hyperplasia of the basophil cells Hare and his coworkers[13] reported a typical case of Cushing's syndrome due to a primary carcinoma of the adrenal cortex with extensive hepatic metastasis The

The first recorded case with necropsy findings was reported by Tilesius[3] This was an instance of a four year old girl who was enormously obese with marked precocious development of the breasts She had marked hirsutism of the body and extremities At autopsy a tumor of the left adrenal was found which had metastasized extensively to the liver Several years later Cooke[4] described another case of a four year old female child who died at the age of seven During this three year period she developed enlargement of the external genitalia the clitoris being nearly an inch in length She developed extensive hirsutism of the genitalia and face her voice became low pitched and the contours of her body approximated that usually seen with puberty During this period of time she became quite obese At autopsy a large tumor probably of the left adrenal was found It is interesting that the cases described by Tilesius and Cooke both had hydrocephalus

The reports of Tilesius and Cooke served to call attention to the role that the adrenals played in the production of this syndrome and in this respect represented the first clarifying aspect of the problem During subsequent years several other cases were reported[5] with autopsy findings It is of interest that up to the beginning of the twentieth century no instances of this syndrome were reported with autopsy findings in males This eloquently bespeaks the preponderance of female children with this unfortunate disease In 1903 Linser[6] described the case of a five year old boy built of adult proportions with thick pubic and scrotal hair The penis was long and the prostate large At atuopsy a tumor of the left adrenal was found The pituitary testes pineal and thyroid glands were grossly and microscopically normal In 1907 Guthrie and Emery[7] reported 2 interesting cases One of these was a boy of four years who had become increasingly stout and had developed a profuse growth of hair over the face back and pubis The obesity was remarkable in that it was limited essentially to the upper half of the body The cheeks were distended and firm with many dilated cutaneous venules There were large lumps of fat involving the shoulders upper extremities and trunk At autopsy a large tumor adjacent to the right kidney was found The pituitary thymus thyroid and pineal glands were grossly and histologically normal The other case reported by these authors was that of a girl of three who presented an identical clinical picture plus the fact that she had many purplish striae over the groins and abdomen When this child died no abnormalities were found in any of the endocrine glands The difference in pathologic findings in these 2 cases is striking and significant in that it called attention to the fact that the adrenogenital syndrome can occur in the absence of any abnormalities of structure noted at necropsy We know however today that the lack of any pathologic changes by no means excludes the existence of abnormalities in function

In 1910 Apert[8] collected a series of 31 cases from the literature characterized by obesity amenorrhea and hirsutism and applied the term Hirsutisme to this group Apert pointed out that these symptoms were frequently associated with tumors of the adrenal cortex Some half a decade later Achard and Thiers[9] described the case of a seventy two year old woman who had a thick moustache and beard hypertension and

signs of acromegaly Nevertheless none will deny the cause and effect relationship between these adenomas and acromegaly

The question concerning the significance of the basophilic adenomas was discussed in some detail by Oppenheimer and his coworkers [9,30] They collected 24 cases of Cushing s syndrome from the literature 18 of which had pituitary basophilic adenomas and 1 a preponderance of basophilic cells without definite tumor formation However of this group of 24 cases 16 had adrenal cortical hyperplasia and in only 4 instances were the adrenals perfectly normal structurally These authors feel that the clinical features of the syndrome are probably dependent upon the adrenal changes To buttress their case further they cite 24 instances of basophilic pituitary adenomas without Cushing s syndrome In none of this group were there any adrenal changes They conclude that adrenal changes are practically essential for the development of the clinical features of basophilism A case reported by Kessel[31] is of interest in the light of this observation The case is that of a girl of seventeen who developed scanty menses hirsutism obesity moon shaped facies striae hypertension polycythemia and a reduction in glucose tolerance in short the typical picture of Cushing s syndrome Following a bilateral adrenal denervation the hirsutism and obesity disappeared The blood pressure and glucose tolerance returned to normal and the patient was physically and mentally well Many months following the operation the patient developed an infection and died At autopsy a basophil adenoma of the pituitary was found In this instance despite the fact that pathologic changes were noted in the pituitary relief of symptoms followed the production of reduced adrenal function Kepler and his coworkers[32] struck a somewhat similar note when they suggested that it was at least possible that adrenal overfunction provoked the growth of the basophil elements in the pituitary and that the clinical picture was predominantly an effect of the altered adrenal function Their thesis was based on instances on Cushing s syndrome in which hyperplasia adenoma or carcinoma of the adrenal cortex was found and in only a small minority of the cases was a basophil adenoma present either alone or in conjunction with the adrenal changes Furthermore successful removal of the offending adrenal tumor invariably resulted in the reversal of the clinical picture to normal [3] However some successful results although few in number have been reported following irradiation of the pituitary [33] Thus Jamin[34] reported the instance of a boy of fourteen with all the signs and symptoms of the disease who recovered completely following radiation therapy directed to the pituitary Similarly one of Cushing s patients[3] showed an extraordinary remission following x ray treatment of the hypophysis The contention of Kepler and his coworkers[32] that adrenal overfunction may possibly provoke the growth of basophilic elements in the pituitary has some experimental basis at least in the sense that the number of basophil cells may be influenced by the status of the adrenals Thus Kraus [4] as well as Crooke and Russell [43] describes a reduction in basophil cells in Addison s disease while Shumacker and Firor[37] describe a similar phenomenon after bilateral adrenalectomy

In 1943 Thompson and Eisenhardt[36] published a follow up report of 98 cases of Cushing s syndrome with autopsy findings collected from the liter

pituitary in this instance showed hyaline changes in the basophil cells although the latter were not increased in number.

Experimentally it is entirely clear that the status of the pituitary influences the size of the adrenal cortex considerably. Smith[15] in 1926 and 1927 demonstrated that experimental hypophysectomy caused atrophy of the adrenal cortex. Houssay and Sammartino[16] demonstrated that in the dog excision of the anterior lobe of the hypophysis resulted in a selective atrophy of the adrenal cortex. Under their experimental conditions there followed considerable atrophy of the zona reticularis and the zona fasciculata although the zona glomerulosa was left relatively intact. Schumacker and Firor[17] found that after hypophysectomy the ability of one adrenal to hypertrophy following the removal of the other was lost. The reverse of these experiments has also been demonstrated. Thus as early as 1909 Delille[18] had observed hypertrophy of the adrenal cortex following injections of pituitary extract. These experiments were corroborated by Emery and Atwell[19] and in a somewhat different fashion by Schneckebier[20] and Anselmino.[21] Clinically we know that the anterior pituitary hyperplasia or pituitary tumor observed in acromegaly is associated with adrenal cortical hyperplasia and conversely Simmonds' disease with some atrophy of the adrenals. Finally we now know that ACTH produces adrenal cortical hypertrophy.

These experiments demonstrate the close relationship existing between the anterior pituitary lobe and the adrenal cortex. It is evident that hypertrophy or overfunction of the anterior hypophysis will result in adrenal cortical hyperplasia. It does not, however, necessarily follow that overfunction of the basophilic elements results in a similar phenomenon. The answer was brought one step closer by the isolation by Collip and his coworkers of an adrenotropic factor from the anterior pituitary, but it remains to be proven that this factor is elaborated by the basophilic cells as suggested by Kraus.[3]

Another approach to the problem concerning the relationship between basophilic adenomas and Cushing's syndrome is the statistical one. In 1903 Erdheim[4] described the basophilic adenomas but he was inclined to regard them as curiosities and devoid of any clinical significance. Branchli[5] studied serial sections of the pituitary of 127 patients. Of these basophil adenomas were found in 4, or 3.1 per cent. None of these patients showed any evidences of Cushing's syndrome. Costello[6] examined 1000 pituitaries of patients who died of a variety of causes—all unrelated to Cushing's syndrome—and basophil adenomas were found in 7.2 per cent. Susman[7] in a similar study of 260 pituitaries found that 3.1 per cent had basophil adenomas.

These data are really much less impressive than they appear to be at first glance. The fact that such tumors are found in patients who present no signs of Cushing's syndrome does not necessarily minimize their significance. Adrenal cortical tumors are not uncommon in postmortem studies in patients who during life presented no evidences of the characteristic syndrome.[28] Similarly in the autopsy studies mentioned above acidophilic tumors of the pituitary were also found,[6] yet none of these patients showed

more striking in the animals injected with antihormone serum. In view of the significance of these cytologic changes it is worth while reporting them in some detail. The pituitary basophilic cells of the injected animals were much larger than normal and the character of the granules had undergone a marked change. In many cells the granules were gathered into large irregularly spaced and sized spherical clumps. There was extensive vacuolation and in many cells the vacuoles had replaced the granular material entirely. Very many of the cells showed liquefied areas indistinguishable from the hyalinized basophilic cells described by Crooke. These authors concluded that the basophilic vacuolation is a characteristic retrogressive phenomenon which the cells undergo when their normal physiology is disturbed, and the Crooke changes are regarded as an aspect of the general granule liquefaction which also appears after experimental thyroidectomy and after castration. Bauer[44] has suggested, but without any definite evidence, that the basophilic hyalinization is secondary to hyperfunction of the adrenal cortex. Only recently Laqueur[45] described the presence of typical Crooke's changes in the pituitaries of patients with a variety of illnesses following the administration of cortisone.

Curious cellular reactions have been noted not only in the pituitary in cases of virilism and Cushing's syndrome but also in the adrenals. In 1933 Broster and Vines[46] demonstrated a specific fuchsinophilic staining reaction in the cells of the adrenal cortex in 18 cases of virilism. This reaction is characterized by the production of a brilliant red color of specific adrenal cortical cells when stained with ponceau fuchsin. The adrenals of normal individuals failed to show this reaction, nor was it present in tumors unassociated with virilism. In careful embryologic studies these authors found that this staining reaction involving the inner and middle zones of the adrenal cortex was present in the male fetus between the ninth and seventeenth weeks and in the female fetus between the ninth and fourteenth weeks. In both sexes the reaction disappeared after the twentieth week. Broster and Vines considered it likely that the granules thus stained were closely related to the male hormone. They felt further that overactivity of the adrenal cortex was dependent not on an increase in the size of the gland or the presence of a tumor but rather on the presence of excessive numbers of these fuchsinophilic staining granules. Their occurrence in instances of virilism has been amply confirmed.[47,48,49,50]

The significance and specificity for virilism of this reaction is, however, subject to serious question. In 5 cases of virilism with Cushing's syndrome reported by Oppenheimer and Silver[50] the typical reaction was found in all instances. However, in 10 control cases of adrenal adenomas found incidentally at postmortem in patients who during life had no evidences of virilism, these authors found similar fuchsinophilic granules in the cortex. Cahill and his coworkers[51] found such granules in the adrenal of dogs, in individuals without virilism, and more marked in instances of adrenal cortical tumors with virilism. Sudds[52] demonstrated these granules in 24 per cent of adult male adrenals and in 28 per cent of female adrenals. Interestingly, they were not apparent in any case under twenty-four years of age. This would suggest that age plays some part in the development of these granules, and, as suggested by Cahill,[53] it is possible that the excess

iture Of this group 60 had pituitary adenomas 49 of which were basophilic 3 chromophobe 1 eosinophil 2 mixed 2 malignant 2 fibroadenomas and 1 an unclassified tumor There were 22 cases of adrenal cortical tumors 6 of which were benign and the remainder malignant There were 3 cases of thymic tumors 1 case of arrhenoblastoma and in 12 instances there were no demonstrable tumors of any gland It is unfortunate that in this otherwise excellent report there are no references to the incidence of adrenal cortical hyperplasia occurring either alone or in conjunction with the other pathologic abnormalities noted It is of interest that the 3 cases of thymic tumors originally reported by Leyton Turnbull and Bratton[37] all showed extensive hyperplasia of the adrenal cortex

Thompson and Eisenhardt[36] conclude that the basic disorder of the disease is an excess of adrenal cortical function with an altered pattern of secretion of the patient s own hypophysis

A new approach to the problem was offered by Crooke[39] In a careful pathologic study of 12 cases of typical Cushing s syndrome this author found a curious hyalinization of the cytoplasm of the basophils with a disappearance of its normal granular structure It is of interest that this group of 12 patients included 6 cases with definite basophil adenomas with thymic tumors and 3 with adrenal cortical disease To emphasize the significance of this observation he examined 350 pituitaries selected at random from patients who showed no evidence of Cushing s syndrome and found slight hyaline changes in only 9 instances He concluded that this hyaline change was the fundamental cause of the syndrome and was an expression of increased physiologic activity of the basophilic cell Interestingly enough these hyaline changes were noted only in the non adenomatous basophilic cells

These observations were subsequently confirmed by Rasmussen[40] who found the same hyaline changes in 8 patients with Cushing s syndrome due to adrenal cortical hyperplasia and carcinoma Thompson and Eisenhardt[36] *examined the pituitaries of 63 patients who died of Cushing s syndrome* and found the characteristic hyaline changes in 58 cases

It is of course difficult to determine the significance of these changes in the basophil cells That they apparently occur consistently in cases of Cushing s syndrome is well verified However it is difficult to conceive of hyaline changes of any cells as evidence of increased physiologic activities Other changes besides those described by Crooke occur in the basophil cells in Cushing s syndrome such as extensive vacuolation[41] But while these latter changes occur in a fairly large variety of physiologic and pathologic states[4] the clinical specificity of the hyaline changes is impressive However experimentally the relationship between the vacuolar and hyaline changes is well demonstrated by the studies of Severinghaus and Thompson[4] They succeeded in inducing vacuolar and hyaline changes in the basophilic cells of the pituitary of the dog indistinguishable from that observed by Crooke in Cushing s syndrome These changes were induced in one set of animals by the injection of crude sheep anterior pituitary extract over a prolonged period of time and in another set of dogs by the injection of suitable antihormone serum Although the results obtained in both groups of experiments were essentially similar they were considerably

adenomas of the pituitary and adrenal cortical tumors have been demonstrated in patients who showed no evidence of either virilism or Cushing's syndrome

How can we correlate this large number of variables and find one common denominator? It is fairly obvious that this cannot be done on a pathologic basis, but it is perhaps possible that it can be explained on a functional basis It has inevitably been impressed upon us that extensive distortions in the physiology of the endocrines can be present without any concomitant gross or microscopic abnormalities of the various glands determined by our present pathologic methods On this basis the absence of any pathologic changes in the presence of a typical clinical picture need not be unduly disturbing Similarly the presence of a tumor of the adrenal cortex or of a basophilic adenoma without the concomitant presence of the syndrome is probably due to the fact that those functions of the involved glands are not altered It may very well be that certain cells of the adrenal cortex for example, perform certain specific functions and unless these cells are directly or indirectly involved no alteration of those particular functions will occur It is thus conceivable to have an adrenal cortical tumor which in one instance will produce the picture of Cushing's syndrome and in another will fail to produce any endocrinologic clinical manifestations It is perhaps erroneous to think of all adrenal cortical cells as hormonologically secretory in character, or secreting the same kind of hormones A similar phenomenon has been observed in the function of the adrenal medulla, where it has been demonstrated that not all the medullary cells secrete epinephrine [61] One is driven to this conclusion to explain those instances of adrenal cortical tumor not associated with the characteristic clinical disturbances

One of the impressive aspects of virilism and Cushing's syndrome is the complete reversal of the clinical picture that follows the successful removal of an adrenal cortical tumor This would suggest that whatever the primary etiology most of the symptoms of the disease are due to altered adrenal cortical function It is argued that the disease is a primary one of the anterior pituitary especially of the basophilic cells with secondary involvement of the adrenal There is no doubt that this is true in a certain number of instances But the fact that carcinoma of the adrenal cortex which cannot be explained as secondary to a pituitary basophilic adenoma frequently produces Cushing's syndrome points to the fact that the disease can originate as primary in the adrenal

In the light of our available knowledge concerning the clinical and experimental effects of cortisone and ACTH we can be reasonably certain that the syndrome is due to hyperfunction of the adrenal cortex This state of hyperfunction may occur idiopathically or it may be due to hyperplasia or tumor of the adrenal cortex, or finally it may arise as a secondary manifestation to hyperfunction of the anterior lobe of the hypophysis The last too may arise idiopathically or may be due to a tumor of the anterior lobe These tumors are usually made up of basophilic cell but are not infrequently due to tumors of other cells of the anterior lobe such as chromophobe [62] acidophil [63,64] tumors of the pars intermedia [65] and unclassified pituitary cell tumors,[12] which through mechanical pressure stimulate the basophilic cells to secrete excessive quantities of ACTH which in turn

of granules found in virilism may be due to the ageing influence of this disease

Blackman[110] suggested that the reticular zone of the adrenal cortex is the zone concerned with the elaboration of sex hormones As evidence of this he presents 9 cases 4 of female pseudohermaphroditism, 1 instance of precocious sexual development, 2 of Cushing s syndrome and 2 of periarteritis nodosa in young women with slight facial hirsutism In all instances the zona reticularis was described as increased in diameter and the amount of pigment present in this layer greater than normal Blackman concluded that the adrenogenital syndrome with its associated excessive secretion of sex hormones is closely related to hyperplasia or tumors of the reticular zone cells

Finally, the hypothalamus has been implicated as bearing some relationship to the pathogenesis of Cushing's syndrome Heinbecker[111] described atrophic changes in the nerve cells of the hypothalamic nuclei in 4 of 5 instances of Cushing s syndrome The fifth case had a malignant adrenal cortical tumor but the hypothalamus was histologically normal All instances showed typical hyalinization of the basophilic cells of the pituitary Of 3 of the 4 cases in which the adrenals were mentioned 2 showed definite hyperplasia of these glands The author of the study concluded that at least 3 primary lesions tumors of the adrenals tumors of the thymus and atrophy of the nuclei of the hypothalamus were probable precursors of the hyalinization of the basophils which in turn produced the clinical picture of Cushing s syndrome

In an attempt to bolster these conclusions experimentally Heinbecker produced lesions in the hypothalamus of the dog similar to those found in the patients The animals developed a marked loss in pituitary basophils and degenerative changes in the remaining ones In addition histologic changes were observed in the thyroid gonads and islet cells of the pancreas of a type which according to the author served to explain many of the symptoms of Cushing s syndrome in the human The adrenals remained entirely normal However none of the dogs developed hypertension osteoporosis or diabetes mellitus

From all this mass of frequently confused and sometimes contradictory data what can we conclude concerning the relative significance of the pituitary and adrenals in the production of virilism and the Cushing s syndrome? Until the disease can be reproduced experimentally no definitive conclusions can possibly be arrived at Our impressions must of necessity remain speculative and subject to revision when more accurate information becomes available

It is important to bear in mind that a typical clinical picture of Cushing s syndrome can be present without any observed gross or microscopic abnormalities of any of the endocrine glands[55] Similarly such a syndrome is often associated with only a basophilic adenoma of the pituitary or only an adrenal cortical tumor either benign or malignant or adrenal cortical hyperplasia The disease is also frequently found in association with a basophilic adenoma and the simultaneous presence of adrenal cortical hyperplasia and even occasionally an actual adrenal cortical tumor[56,57,58,59] Instances of the disease are reported in which a malignant tumor of the adrenal cortex is associated with pituitary hypoplasia[60] Finally basophilic

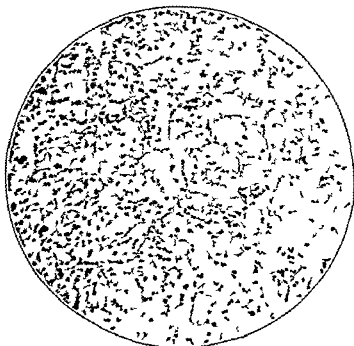


FIG 17 —Photomicrographic section of an adrenal cortical adenoma removed at operation and producing the typical picture of Cushing's syndrome

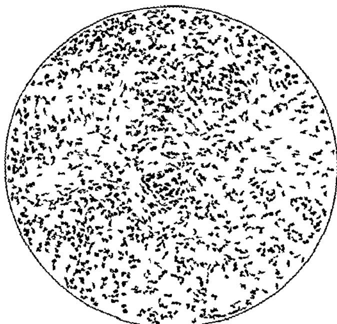


FIG 18 —Photomicrographic section of an adrenal cortical carcinoma producing Cushing's syndrome

increases adrenal cortical activity. Finally, most of the manifestations of the syndrome may be produced in humans by the prolonged administration of large amounts of ACTH or cortisone.

Tumors involving the adrenal cortex may be either benign or malignant. Geschickter[66] reviewed the pathology of 72 instances of adrenal cortical tumors and found that only 6 of this group were malignant. This is somewhat misleading in that 63 of this group were totally asymptomatic. Generally speaking, the asymptomatic adrenal cortical tumors are benign and are found only incidentally at autopsy studies. The incidence and significance of this kind of tumor can be appreciated from Goldzieher's studies,[8] who found that 35 per cent of the adults who came to postmortem had adrenal cortical nodules which were apparently symptomless. The incidence of malignancy of adrenal cortical tumors producing symptoms is considerably higher. In those in which the symptoms produced are nonhormonal in character, almost all are malignant,[53] while in the instance of the hormone producing tumors fully half are of a malignant character.[66] Occasionally such malignant tumors are bilateral.[67] Adrenal cortical tumors arising in adrenal rests have been reported.[68, 69] Such accessory adrenal tissue may be located anywhere from the testicle to the kidney in the male, and from the ovary to the kidney in the female. Tumors arising in these rests are capable of producing the hormonal changes characteristic of the more orthodox adrenal cortical growths.

Signs and Symptoms of Tumors and Hyperplasia of the Adrenal Cortex.—It is important to emphasize once more that not all tumors of the adrenal cortex produce symptoms and that some adrenal cortical tumors are nonhormonal in character and manifest themselves by those signs and symptoms referable to any large retroperitoneal mass.[53, 70]

Non-Hormonal Adrenal Cortical Tumors Producing Symptoms.—These tumors usually occur in adults, are equally distributed between both sexes and are generally malignant. Occasionally such tumors will develop in aberrant adrenals. Signs and symptoms of the nonhormonal adrenal cortical tumors will not appear until the tumor is large enough to produce symptoms by virtue of its size or until metastases have occurred. Unfortunately, by the time symptoms appear the total erradication of the tumor is usually impossible because of the presence of metastatic lesions elsewhere. The presenting symptoms are usually pain in the abdomen or flank frequently made worse by bending, malaise, loss of weight and occasionally fever. On physical examination a non-tender firm mass may be palpable in either flank. This mass is frequently mistaken for kidney or spleen, but retrograde pyelographic studies or perirenal insufflation will often demonstrate the true character of the mass. Metastases are usually found in the *liver, lungs, retroperitoneal lymph nodes* and occasionally in the kidneys.

These adrenal cortical tumors are not associated with hypertension, obesity, hirsutism or any of the other signs characteristic of the hormone producing tumors. The urinary 17-ketosteroid excretion in these instances is within the normal range. The operative procedure for the removal of the tumor is not fraught with any undue hazard in these patients and special preoperative precautions such as are essential in patients with hormone producing adrenal cortical tumors are not necessary.

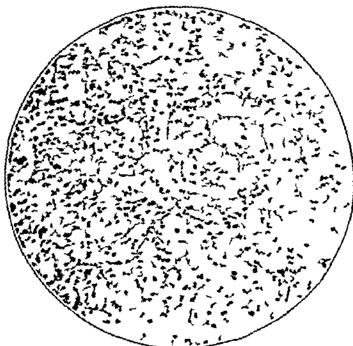


Fig 17 —Photomicrographic section of an adrenal cortical adenoma removed at operation and producing the typical picture of Cushing's syndrome

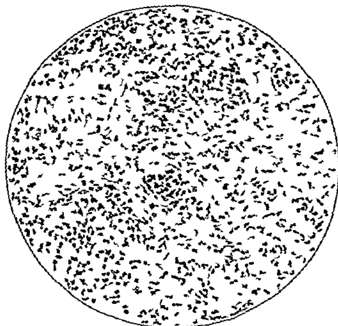


Fig 18 —Photomicrographic section of an adrenal cortical carcinoma producing Cushing's syndrome

Hormone Producing Adrenal Cortical Tumors or Hyperplasia.—We can divide the signs and symptoms of these tumors into two large categories 1 those with sexual changes, and 2 those associated with certain metabolic abnormalities not related to the sexual alteration The first group of symptoms is referred to as the adrenogenital syndrome and the second category is known as Cushing's syndrome It should be stated at once that this division is a purely arbitrary one and that considerable overlapping occurs It is perhaps not uncommon to find patients who present only the adrenogenital syndrome but it is extraordinarily rare to find instances of adrenal cortical tumor or hyperplasia manifesting only those metabolic disturbances classed as Cushing's syndrome In certain groups of patients signs of virilism or evidences of sexual changes may be overshadowed by the greater prominence of the metabolic disturbances this being particularly true of adult males who develop adrenal cortical tumors but in almost all instances some signs of sexual alterations are evident

Roughly, the symptoms and signs referrable to the first group are pseudohermaphroditism precocious sexual and physical development hirsutism, amenorrhea impotence change in the character of the voice and a tendency to sex reversal The findings in the second group include a curiously disposed obesity osteoporosis, hypertension decreased glucose tolerance purplish striæ polycythemia dusky cyanotic discoloration of the skin aceneform eruptions and a tendency to purpura and ecchymoses

The nature of the clinical manifestations will depend on the sex and upon the age of the patient when the disease develops Although the disease may occur at any age it is most common up to and including early adult life Cases have occurred in women after the menopause and in men in the fifth decade of life The disease is however considerably more frequent in females than in males the ratio being approximately 4 1 [7, 71]

The Congenital Form of the Disease.—When hyperplasia develops in utero pseudohermaphroditism will result For purposes of clarification it may be well to point out that true hermaphroditism or hermaphroditismus verus is characterized by the presence of the gonads of both sexes in the same person In addition in the classical sense the external genitalia of both sexes are also present in the individual Actually this pure and complete form of true hermaphroditism is only a theoretical possibility and it is highly questionable as to whether such a complete case ever existed [7] In any event the reported cases of true hermaphroditism have been characterized by the simultaneous presence of the gonads of both sexes and some variations and abnormalities of the external genitalia

True hermaphroditism is an embryologic developmental defect and in contrast to most instances of pseudohermaphroditism is not related to abnormalities of the adrenal cortex

Pseudohermaphroditism is characterized by the presence of the gonads of only one sex but associated with this are such abnormalities of the external genitalia as to render the identification of the sex through external examination doubtful Male pseudohermaphrodites are those individuals whose gonads are testes while female pseudohermaphrodites have ovaries

The classification into male and female pseudohermaphroditism is entirely independent of the nature of the external genitalia. The final determination of the sex frequently requires surgical inspection of the pelvic organs.

Young[7] reported instances of male pseudohermaphroditism in which the genital abnormalities varied from a hypospadic phallus with partially descended testes, cleft scrotum, pseudo-vulva and female type urethra to an instance in which a uterus, tubes, two pelvic testes and a vagina opening into the urethra were present. All sorts of variations between these two extremes have been reported.

The female pseudohermaphrodites usually present an enlarged clitoris which looks like a hypospadic penis. The vagina may not be completely descended and may open into the urethra. The presence of prostatic tissue has been frequently noted,[73] while the ovaries, uterus and tubes remain rudimentary. In the female pseudohermaphrodite hirsutism and a tendency to a male configuration of the body are usually encountered. Interestingly enough, the asexual metabolic disturbances characteristic of Cushing's syndrome are not observed in the young pseudohermaphrodites.

The incidence of pseudohermaphroditism is approximately 1 in 1000 individuals, according to Young.[72] Neugebauer,[71] in analyzing over 1200 case reports from the literature, found that male pseudohermaphroditism, that is individuals having the male gonad, was 7 times as common as female pseudohermaphroditism.

Marchand was the first perhaps to point out the association of pseudohermaphroditism with hyperplasia of the adrenal cortex. This was subsequently confirmed by Glynn[73] and today it is recognized and accepted that female pseudohermaphroditism is due to disease of the adrenal cortex, usually hyperplasia involving both glands. It is interesting that while the relationship between adrenal cortical hyperplasia and female pseudohermaphroditism is well established, the cause of male pseudohermaphroditism is still obscure. Most instances of pseudohermaphroditism with proven adrenal cortical hyperplasia have been observed in patients with female gonads and it is questionable as to whether a similar cause and effect relationship is applicable to the male. On a purely theoretical basis it is difficult to envision two identical highly specific clinical abnormalities which have not the same common pathologic basis. It is possible that there is adrenal hyperfunction in the male pseudohermaphrodite without concomitant hyperplasia of the adrenal cortex. This phenomenon might conceivably occur in the presence of active testicular tissue.

Pseudohermaphroditism is consistent with a long although somewhat confused life span. The case reported by DeCrecchia[78] lived to the age of forty three, while Lucett's case lived to the age of seventy.[79] The former patient lived his entire life except for the first four years as a male. He had a typical male configuration with extensive and heavy hirsutism. His penis was 6 cm in length and he apparently conducted an active male sexual life since he contracted gonorrhea twice. At autopsy, however, a prostate, uterus and ovaries were found. There was no evidence of any testicular tissue. Both adrenal cortices were markedly hypertrophied.

Fibiger[80] reported 3 cases of female pseudohermaphroditism, 2 of which are extremely interesting. The first of these was a fifty-eight year old

'man who died of pulmonary tuberculosis He had a heavy beard his penis was 5 cm in length and his habits were entirely masculine The true nature of his sex was not determined until an autopsy was performed when uterus tubes ovaries and a vagina opening into the urethra were discovered In addition prostatic tissue of apparently normal size and thickness was found The adrenals were enlarged and there was no evidence of any testicular tissue Finger's second case was perhaps even more interesting This was a forty seven year old male who had been married to a woman for twenty-eight years and had apparently led a normal sexual life At autopsy following death from pneumonia uterus tubes and ovaries were found to be present although these organs were small and underdeveloped The vagina opened into the urethra the latter being surrounded by prostatic tissue There was a penis like organ of fairly good size The adrenal cortices were markedly hypertrophied

Young[7] describes a case of female pseudohermaphroditism who lived as a male until the tragic termination of his life This patient was originally seen at the age of eleven and was found to have a hypospadic penis labia majora and a perineal opening of the urethra During the exploratory laparotomy well formed tubes ovaries and uterus were found There was no evidence of any testicular tissue Physically the patient looked like a well-developed boy somewhat older than his chronologic age *The voice was coarse there was hair on his face and upper lip* although the pubic hair was of female distribution The breasts were of the male type while the pelvis and thighs were of female contour No testes were present either in the scrotum or groin Despite the fact that this patient was conclusively demonstrated to be a female pseudohermaphrodite his parents continued to rear him as a male At the age of fourteen he developed a moustache and at the age of sixteen he began to have frequent coitus with women averaging 2 or 3 times a week The coitus was always accompanied by ejaculations

By the time he reached the age of thirty one he had established himself as a successful business man He had the appearance of a short but well formed man He had fallen in love with an attractive woman with whom he led an apparently normal sexual life His attempt to marry his fiancee was frustrated by his religious advisor who was aware of the true nature of his sex In despair he committed suicide and at autopsy the previous findings determined during the early exploratory procedure were confirmed *In addition both adrenals were found to be markedly hypertrophied*

For purposes of comparison it may be desirable to describe a case of male pseudohermaphroditism also reported by Young[7]

'Mrs W C aged twenty-six years divorced had been reared as a female At the age of eighteen the patient was in love with a man noticed erection of the clitoris which became very large on sexual excitation She demanded that her physician remove the clitoris The vagina was small and short Swellings thought to be hernia were found in the groins On examination a clitoris about 4 cm long a short vagina and inguinal hernia on each side were discovered After amputation of the phallus under local anesthesia an incision was made in the groin to cure the hernia The surgeon was astounded to find that a testicle was present An incision in the opposite groin disclosed another

testicle The operator then told the patient that a great mistake had been made that she was undoubtedly *a male* that the swellings in the groins were testes and that the enlarged clitoris which had been amputated was really a penis *The patient declared that she did not want to be a male and ordered* the physician to remove the testes She then married her fiancé and they lived *together for a period of two years after which he left her* During this time the husband had apparently no complaints and they both enjoyed coitus The patient subsequently had coitus with other men and finally became engaged to another man *The face and upper part of the patient were* distinctly masculine There was a light beard and no breasts The lower half of the body and hips were feminine The vagina was 5 cm long *The cervix* was absent On rectal examination the vagina was palpable but neither pro*state nor vesicles* could be made out

The adrenal cortical hyperplasia associated with female pseudohermaphroditism generally occurs early *in prenatal life* When the adrenal hyperplasia *occurs* late in the congenital period virilization in the female and macrogenitosomia praecox in the male may be encountered Occasionally this type of adrenal cortical hyperplasia is associated with adrenal insufficiency This is more frequently *encountered* in the male than in the female The *adrenal insufficiency* is *manifested* solely by loss of *electrolyte* and water Indeed the urinary excretion of the neutral 17 ketosteroids is markedly *increased* while that of the 11-oxygenated steroids *is essentially* normal Recently it has been reported that the urinary excretion of the *neutral 17 ketosteroids in this group may* be diminished *following the* administration of cortisone

Adrenal Cortical Tumors and Adrenal Cortical Hyperplasia Before Puberty —In children the presence of adrenal cortical tumors or hyperplasia may either induce a markedly precocious obesity or excessive muscular development the so-called infant Hercules type[10] Generally speaking the former group may be observed *in* both sexes while Herculean development is encountered mostly in boys Occasionally *one* observes intermediate forms consisting of a combination of both the fat and muscular types[illegible] The intermediate form occurs in children of both sexes It was originally assumed that children with adrenal tumors or hyperplasia rarely manifested the metabolic disturbances characteristic of Cushing's syndrome Actually this syndrome is not uncommon in the adrenogenital group in children and Farber and his group[illegible] have collected 26 such cases from the literature and in addition have reported 1 of their own The so-called obese plethoric type certainly presents many of the characteristics of the typical Cushing's syndrome In children presenting the adrenogenital syndrome tumors of the adrenal cortex usually malignant[illegible] are more frequently encountered than adrenal cortical hyperplasia This is in rather striking contrast to that observed in *pseudohermaphroditism* where *adrenal cortical hyperplasia is the rule*

The adrenogenital *syndrome in female children is characterized by* sexual precocity the development of *hirsutism of the face and limbs* enlargement *of the external genitalia* and deepening of the voice *In most instances* there is a temporary *period* of rapid growth which is however followed by an early closure of the epiphyses The end result is usually a rather short individual *Menstruation as a rule* does not occur even in

older children who may have reached the age of puberty although several notable exceptions have been reported [3, 81] In general in both boys and girls the clinical picture is that of a rapidly ageing process in which, during the span of a few short months or years, the child had developed physically into an adult

Obesity is usually a common finding in this group, and may attain enormous proportions The distribution of the obesity is rather interesting in that it characteristically involves the face, trunk, and abdomen, the extremities remaining relatively thin The face assumes a full moon like appearance while pads of fat appear in the upper dorsal region over the



Fig 19 —Female child aged 1 year with Cushing s syndrome due to adrenal cortical tumor

shoulders chest and in the flanks The abdomen may become markedly protuberant The appearance of the child may be monstrous due more to the curious disposition of the fat than to an actual gain in weight [85] However, not all children with the syndrome conform to the characteristic pattern The obesity may be evenly distributed or there may be actual emaciation Lightwood[86] reports the instance of an eighteen week old infant with a tumor of the adrenal cortex who developed considerable wasting while at the same time retaining marked deposits of fat about the face and chest In addition the child may develop other evidences of Cushing s syndrome Such a case was reported by Elizalde[87] and quoted by Anderson and Haymaker [88] It is worth while recapitulating the significant data observed in this case as reported by Anderson and Haymaker since it represents in a sense the classical picture of the adrenogenital and Cushing s syndrome as observed in female children

A girl who at the age of three suddenly and rapidly gained in weight and strength Her face neck trunk abdomen and proximal aspects of her limbs became obese A heavy growth of hair developed on the face body and extremities She was obliged to shave her moustache and beard The appetite became ravenous She developed the raucous voice of a man At school she was gentle and reserved and bright When seen at seven years of age she was excessively developed for her age Her masculinity and adiposity gave her the configuration of a male The face was reddish plethoric and puffy The voice was masculine She weighed 92 pounds the weight of a normal fourteen year old girl Striæ atrophica were present over the abdomen axillæ and thighs The pubic hair was that of an adult woman There were numerous acneform lesions of the skin The labia majora were much enlarged while the labia minora were atrophic The clitoris was 2 cm long and erectile The uterus was very small The skeleton was of the virile type with a narrow pelvis The milk teeth were well formed The bone age was fourteen to fifteen years Glycosuria was present In addition the blood pressure was 150 90 pulse 93 hemoglobin 121 per cent and the red blood cell count was 6 000 000

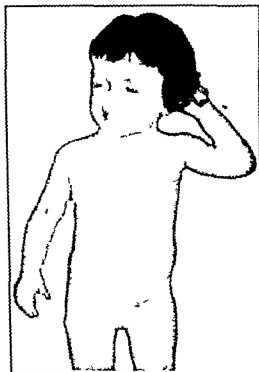


Fig 20 —Child shown in figure 19 one year following successful removal of adrenal cortical tumor

As we review this case we recognize that the clinical manifestations fall into two groups The signs of virilism which are normally associated with the adrenogenital syndrome and characterized by rapid growth and ageing the hirsutism change in the character of the voice and the enlargement of the clitoris represent the dramatic aspects of the disease In addition there are the more subtle metabolic disturbances the obesity plethora

acneform eruption, striae atrophicae, hypertension, and glycosuria commonly associated with Cushing's syndrome.

It must be emphasized that this classical and complete combination is by no means always or even frequently encountered in children. More commonly one observes instances characterized by rapid growth, obesity, and evidences of precocious sexual development with an absence of the other signs of Cushing's syndrome. Occasionally the striking manifestation is a startling obesity limited to the face, neck, chest and flanks associated with only a moderate hirsutism and relatively slight genital hyperplasia. In addition there may be severe hypertension. Such an instance was observed in our clinic.

The patient was a one year old female infant who was admitted to the hospital because of obesity and slight hirsutism. The latter was originally noted at the age of three or four months as a light fuzz over the face, the back and the pubis. There was no further increase in hair until the age of ten and one half months when the hirsutism in these areas increased somewhat. At the age of seven months unusual fullness of the face was noted and since then obesity had become more marked and diffuse. Interestingly enough there was some retardation in general growth and during the past six months the heel to crown length had barely altered. There were no particular genital abnormalities except for a moderate increase in the size of the clitoris. The blood pressure was consistently and markedly elevated and on several occasions was found to be 240/180. The white blood cell count was 12 300 with a normal differential. The hemoglobin was 96 per cent while the red blood cell count was 4 500 000. A glucose tolerance test revealed a control blood sugar level of 80 mgm per cent with a steep rise to 200 mgm per cent one hour after the administration of glucose. At the end of two hours the blood sugar was still 170 mgm per cent but after three hours it had returned to the control level. The blood sodium was elevated to 150 9 milliequivalents per liter while the blood chlorides were 105 and the potassium 5 6 milliequivalents per liter. There was a moderate increase in the urinary excretion of the neutral 17 ketosteroids 4 mgm being excreted in twenty four hours. X ray studies of the skull were essentially negative but the remainder of the bony skeleton showed some questionable slight diffuse osteoporosis. Intravenous urography including sectional radiography revealed the right kidney to be displaced caudad with the suggestion of a mass about the size of a small lemon above the kidney.

It was evident that the child had an adrenal cortical tumor. She was accordingly prepared with hog adrenal cortical extract, whole adrenal cortical extract, and parenteral fluids and operated upon. A well-encapsulated adrenal cortical tumor approximately the size of an apricot was removed from the right side. The parenteral fluids and extracts were continued for several days postoperatively. On histologic study most of the tumor appeared to be benign but there were several suspicious areas in which malignant changes seemed to have occurred.

Within three weeks after operation the child appeared to be quite well. The blood pressure had gradually fallen and now seemed to vary between 100/60 to 140 80. The glucose tolerance curve now showed a maximum rise to 100 mgm per cent one half hour after the administration of glucose and returned to the control level within an hour. The urinary excretion of the neutral 17 ketosteroids was reduced to less than 1 mg per twenty four hours. Both the moon like facies and the hirsutism were less pronounced and tending to disappear.

Adrenal cortical tumors or hyperplasia in boys may be characterized by obesity, marked muscular development or both. According to Harris and

Pflews[89] the "infant Hercules" type in which the muscular development attains considerable proportions occurs in more than half the cases

The incidence of the adrenogenital syndrome with or without the association of Cushing's syndrome is extremely rare and occurs even less frequently in boys than in girls However the clinical manifestations are essentially similar These male children grow rapidly and develop signs of virilism with extensive hirsutism of the face pubis and frequently the rest of the body There is marked precocious sexual development which unlike that observed in girls is homologous in character Feminization has been reported in but 1 instance in association with a benign adrenal cortical tumor [14] The size of the genitals may assume adult proportions The genital maturation need not be associated with adult potency [90] although Lisser[91] and Cahill and his coworkers[53] have reported the occurrence of spermatogenesis Muinzer's patient [?] a boy of eight actually acquired a venereal infection through the usual channels The enlargement of the penis may or may not be associated with a corresponding increase in the size of the testes and prostate

The case reported by Guthrie and Emery [7] is an excellent example of the obese type of adrenogenital syndrome in the male child

This was a boy of four years whose symptoms apparently dated back for a period of two years During this period he had become increasingly stout The cheeks were enormous and distended of a firm consistency and bright red in color The cutaneous venules were dilated and very much in evidence The shoulders trunk and upper extremities were laden with fat which hung down in pendulous folds about the breasts and flanks and formed a huge lipoma in the upper part of the back The obesity was essentially limited to the upper half of the body while the lower half appeared quite normal for a child of his age The child was 36 inches tall and in addition to the obesity had a considerable hirsutism of the face back and pubis The eyebrows were thick and bushy The child was bright probably in advance of his chronologic age He died at the age of five and at autopsy a tumor probably a carcinoma of the right adrenal was found

In Lenser's patient [6] obesity was much less marked while the child physically attained fairly adult proportions

This is the case of K K a boy of five years of age who could easily pass for sixteen or eighteen years He was fifty four inches tall and weighed 86 pounds He had thick pubic and scrotal hair The penis was 9 cm long and the prostate was quite large This child was strong and could easily lift a 44 pound weight He was reported as being mentally retarded When the child died a tumor probably malignant of the left adrenal was found

These two children are examples of the adrenogenital syndrome in which obesity in one instance and marked muscular development in the other were the outstanding manifestations Both had virilism but neither presented the typical picture of a Cushing's syndrome The case reported by Farber Gustina and Postloff[81] is characteristic of the third group of adrenogenital syndrome observed in both boys and girls in which a full blown Cushing's syndrome is present in addition to the virilism

The case reported by the above authors is that of a boy of fifteen years whose symptoms apparently started one year previously with a rapidly acquired obesity and a progressive generalized weakness and fatigue This

ical examination on admission revealed a well developed obese white boy, who was moderately dyspneic. He complained of severe low backache whenever a change in position was attempted and was unable to sit up because of his extreme general weakness as well as the pain associated with motion. The obesity was confined to the face, neck and trunk, the extremities were spared. He was 170 cm in height and weighed 62.5 Kg. His face was florid, greasy and hairy, and there were a few small areas of telangiectasis. Examination of the eyes showed the optic disks to be normal. There was no evidence of papilledema, exudates or hemorrhages. The examination of the visual fields showed some mild peripheral contraction more evident in the right eye. The blood pressure was 184 mm of mercury systolic and 112 mm diastolic. The external genitalia were large but otherwise normal in appearance. There was considerable tenderness on pressure over the lumbar vertebrae. On the lateral and anterior surfaces of the thighs and flanks and to a lesser extent on the legs were many purplish striae cutis distensae. The entire osseous system, especially the skull and the spine showed severe osteoporosis. The skull had a ground glass appearance and the sella turcica was of normal size. All of the lumbar vertebrae showed narrowing of the bodies due to expansion of the nucleus pulposus.

The blood counts of this patient revealed a considerable increase in the hemoglobin content of the blood, while glucose tolerance tests on at least two occasions yielded curves pointing to decreased utilization of the ingested sugar. Retrograde pyelograms and perirenal insufflation revealed the presence of a large mass obscuring the upper pole of the right kidney. Following operation, in which a tumor of the right adrenal was found and removed, the patient died. On histologic study the tumor was identified as a cortical cell carcinoma.

When we examine the details of this case we find that it differs from the other two instances quoted in that the predominant manifestations were the curious metabolic disturbances characteristic of Cushing's syndrome. There were some evidences of virilism, such as an increase in hirsutism, size of the genitals and a general increase in physical development beyond that expected of a boy of his age. But these evidences of the adrenogenital syndrome were overshadowed by the metabolic disturbances. It is worth while noting the more rapid and fulminating course pursued by this patient in contrast to the others. It is in general true that children with an adrenogenital syndrome who present many of the characteristics of Cushing's syndrome not only constitute a much more serious operative risk but run a more rapid course which usually terminates fatally unless successfully operated upon. Very rarely there will occur a spontaneous remission of the disease *which may last for many years and perhaps indefinitely*. One such case was reported by Cushing.[1] The patient was lost sight of after some twenty two years of observation. When such spontaneous remissions occur it is probably in those patients who have no adrenal cortical tumors.

Adrenal Cortical Tumors and Hyperplasia in Adults. — The clinical picture produced by hormonal secreting adrenal cortical tumors or hyperplasia differs in men and women. In women the general tendency is to virilism with the appearance of secondary male characteristics, while in men there is rarely any increase in virilism but rather often a slight and occasionally a marked feminization.

The Manifestations of the Disease in Women. — Women afflicted with the disease may manifest predominantly the adrenogenital syndrome, the Cushing's syndrome or a combination of both. The last is the most com-

mon clinical picture observed. The syndrome is considerably more common in women than in men,[93] and may occur at any age between puberty and the menopause. Most instances are observed between the second and fourth decades of life, although some cases occurring after the menopause have been reported.[94]

The adrenogenital syndrome in women is characterized by virilism with the appearance of secondary male characteristics and the suppression at least of many of the female characteristics. The earliest manifestation is usually the development of hair over the face and extremities, and an increase of pubic hair acquiring a male pattern. The hirsutism of the face is usually extensive and frequently the patients develop a well-defined moustache and beard that require daily shaving. The hair may be fine and silky in character having the appearance of lanugo, or it may be long and coarse and thick. Coincidental with the appearance of the hypertrichosis or directly before or after, there occurs an alteration in the menses. They become scanty and infrequent and eventually cease entirely. Associated with this there frequently occurs a diminution in libido and occasionally even a transfer of sexual interest to other females. There occurs atrophy of the breasts and a diminution of chest and hip fat. The muscles of the extremities tend to become more pronounced, and the entire physical configuration tends to assume the male form. The clitoris may hypertrophy considerably, the labia darken in color, while the uterus and ovaries tend to shrink somewhat in size. The voice deepens and becomes harsh in quality, probably due to thickening and elongation of the vocal cords. Such a case was reported by Holmes.[9]

This was a young woman of seventeen years of age whose menses ceased abruptly. Two years later fine hair appeared on the chin and upper lip, slowly becoming longer and more profuse until at the age of twenty-three it had spread over the limbs, trunk, neck, and cheeks. Pubic hair extended up the abdomen. She gradually lost weight and the breasts became small. The subcutaneous fat around the hips was considerably reduced, and she began to look like a boy of poor physique. The clitoris became very large and the uterus small. The voice had not changed in character. At operation a large benign adrenal tumor was successfully removed. Thirty-six days after the operation she menstruated for the first time in nine years. When she was seen six years later her menses had become perfectly regular, the abnormal hair had disappeared, her figure assumed the normal female configuration, while the clitoris diminished to normal proportions.

Cahill and his group[53] report a similar case.

Case R. P., an eighteen year old girl, was seen in 1939 complaining of hair on face and body and lack of menstruation. She had had normal menses from the age of twelve up to five months before admission. She then missed one period which was followed by a scanty period and there had been none since. At the same time hair appeared on her upper lip, chin, cheeks, chest and buttocks. Hair grew long upon her arms and legs and became darker. Her voice deepened. She had no pain or any other symptom. Her figure resembled a young male adult with male hair distribution. There was a hypertrophy of the clitoris and slight hypertrophy of the labia. The pelvic organs were normal except for a loss of usual ovarian sensitivity. There was no hypertension. The blood counts and the blood chemistry were normal. Basal metabolic rate, visual fields, and glucose tolerance tests were normal. X-ray film of skull, chest, and abdomen showed no abnormality. Air insufflation roen-

genograms showed an ovoid tumor of the outer portion of the left adrenal The right adrenal appeared normal At operation an ovoid tumor of the outer portion of the left adrenal was resected from the inner or normal portion through a left oblique transperitoneal approach She made an uneventful recovery Her menses returned to normal two months after operation Following the operation her breasts increased and the hair became less upon her body Her voice became higher pitched She progressed without change in her menstruation but the hair remained upon her chin and neck An air insufflation X ray film of her untouched right adrenal taken in 1940 showed that the lower end had become rounded and wider In March 1941 she noticed that menses had become scantier and that her hair growth was somewhat more vigorous She was readmitted to the hospital and insufflation air x ray films were taken showing that the lower end of the right adrenal had become rounded and resembled a tumor

She was again operated upon in April 1941 and an ovoid tumor the size of a plum was resected off the lower pole of the right adrenal through a lumbar incision She made an uneventful recovery Following the operation she resumed her normal menstruation with the exception that they were accompanied by premenstrual pains the first that she had had since the cessation of menses previous to the onset of the left adrenal syndrome

These 2 cases epitomize the clinical picture of the pure type of adrenogenital syndrome occurring in women and due to an adrenal cortical tumor Note the absence of any metabolic disturbances characteristic of Cushing s syndrome The main clinical manifestations are those of virilism with a reversal of the secondary sex characteristics Associated with these physical changes are psychologic changes in which the outlook of the patient alters considerably Her interest in male companions is reduced and homosexual trends are often manifested Women with this form of virilism are generally non fertile The response to successful surgery is however startlingly dramatic There occurs not only a change in the physical characteristics of the patient with a reversal to the normal female state but the mental and sexual outlooks again become feminine With recovery and resumption of the menses these patients are able to conceive and pregnancies have been reported after operation [96 97]

It is important to observe too the relative ease with which these patients may be successfully operated upon in contrast to those patients manifesting Cushing s syndrome The reason for this resides in the fact that the presence of adrenal tumors in the former group is never associated with a compensatory atrophy of the contralateral adrenal an unfortunate state so often met with in patients manifesting the signs and symptoms of Cushing s syndrome The clinical course in general of women with the adrenogenital syndrome is quite different from that of those with Cushing s syndrome although an adrenal tumor may be present in both The former group of patients pursue a prolonged course extending over many year and even if not operated upon their life span need not be particularly influenced

Tumors of the adrenal cortex producing virilism are rare but there are a large number of women who have some facial hirsutism with perhaps scanty menses and rather small atrophic breasts Chemical and roentgenologic investigation of this group fails to reveal any adrenal abnormalities These patients differ from those with tumors in that the manifestations of virilism are by no means as marked nor is the general clinical picture

nearly as striking. *It is possible that in this group too the adrenals may at least be theoretically implicated although such involvement cannot at present be demonstrated.* It is important to recognize this group and to separate them from those with tumors in that they require no particular therapy nor are any therapeutic measures available for them at present. They are capable of fulfilling the normal feminine functions and the physical abnormalities which they manifest are essentially of cosmetic concern.

The metabolic disturbances of Cushing's syndrome are characterized by obesity, hypertension, osteoporosis, purplish striae of the skin, acne, polycythemia, alterations in carbohydrate metabolism, cyanosis and purpura or ecchymoses. In addition these patients often manifest marked asthenia, polyphagia, polydipsia, polyuria, mental changes and occasionally pigmentation of the skin reminiscent of that seen in Addison's disease.

The typical patient with Cushing's syndrome will manifest all or almost all of the signs and symptoms mentioned above. Not infrequently, however, a modified picture is present in which the outstanding characteristics are those of virilism with some of the manifestations of Cushing's syndrome. Thus Cahill and his coworkers[51] described a case probably of adrenal cortical hyperplasia which presented marked obesity in addition to virilism.

> This was a girl of twenty who had a perfectly normal childhood until the age of twelve and a half when menses began. Concomitant with this she began to gain weight. Her periods were regular for five months and then ceased. There occurred a heavy growth of hair on her head, some on the cheeks, upper lip and chin, and marked hirsutism of the arms and legs. The pubic hair was masculine in distribution. The breasts were medium sized, and the abdomen was pendulous. The blood pressure was 170/30. A perirenal insufflation showed that both adrenals were remarkably enlarged although normal in outline. When this patient came under observation of the authors her weight was 301 pounds and she was 65 inches in height.

Koster *et al.*[93] described an even more remarkable case which responded well to surgery.

> The patient, a female, at the age of twenty three weighed 335 pounds. The history of the onset of the disease apparently dated back to the age of thirteen when during the course of one year she gained 75 pounds and continued to gain progressively thereafter. In addition to the obesity she had hair on the chest, face, abdomen, forearms and legs, and a masculine distribution over the pubis. Her voice was deep and rough. She had marked diurnal and nocturnal urinary frequency. The blood pressure was 105/62, but she had a slight polycythemia. At operation both adrenals were found to be enlarged and one was removed. Within one year after the operation she lost 145 pounds.

It must be emphasized that the obesity in this disease is generally not as extreme as described in the instances cited above. A gain in weight, however, is common and it is usually associated with a rather characteristic distribution of the adipose tissue. The obesity is essentially confined to the face, shoulders, trunk and abdomen while the extremities remain relatively thin. The increase in facial fat produces the typical moon-like facies.

The usual picture produced by an adrenal cortical tumor is exemplified by the following case.

The patient was a female aged thirty seven who was well until two and one half years prior to admission to the hospital At the time of the onset of her illness she noticed a slight but definite decrease in visual acuity A year later she began to develop large ecchymotic areas over the lower extremities which recurred at frequent intervals Two years after the onset of her symptoms she noticed a change in the appearance of the face Her face became round puffy plethoric with coarsening of the features and marked hirsutism During this period of time she developed amenorrhea On physical examination she was found to be very obese but the obesity was limited essentially to the face neck shoulders and abdomen The upper and lower extremities were surprisingly thin She had many *purplish striæ over the abdomen and large ecchymotic areas over the lower extremities* Pelvic examination failed to reveal any adnexal masses There was considerable enlargement of the clitoris however The blood pressure was 154/114 The blood hemoglobin was 105 per cent red blood cell 5 4 million The white blood cell count and differential were normal The oral glucose tolerance test employing 1 75 grams *of glucose per kilogram of body weight yielded the following results* Control 70 mgm per cent one-half hour 150 one hour 250 two hours 175 three hours 210 four hours 110 and five hours 65 mgm per cent The serum cholesterol was 230 calcium 8 8 and inorganic phosphorous 2 9 mgm per cent The blood phosphatase was 9 4 K A unit The urine frequently showed traces of sugar X ray studies showed a normal sella marked osteoporosis *of the entire spine and an old fracture of the left fifth rib in the anterior axillary line* Perirenal insufflation revealed a mass on the left side above the kidney and on operation a left adrenal cortical tumor the size of a plum was removed

The following cases have previously been reported by Oppenheimer and Silver[30]

The first patient was a woman of thirty four who had been well until several years prior to admission to the hospital when her periods became irregular and somewhat scanty The metrorrhagia at one time became so pronounced that a curettage was performed After the curettage amenorrhea developed which persisted until the time of admission to the hospital One year after the cessation of the menses she noted that her face was swollen and puffy and that she had gained 8 pounds in weight She began to manifest exertional dyspnea and ankle edema Her physician observed the presence of sugar and albumin in her urine More recently her face had become ruddier and facial hirsutes had appeared although not markedly so Purpuric spots then appeared on her arms and legs and some purplish striæ on the abdominal wall

The physical examination revealed the presence of the moon like facies so characteristic of this disease There was no definite obesity but the arms *and legs were strikingly thin in contrast to the rest of the body* The face was flushed and numerous telangiectasis were present The eyes were moderately prominent The retinal arteries were narrow irregular in caliber and indented the veins The disk margins were sharp The neck was thick and bull like The heart was enlarged to the left The abdomen was moderately obese The clitoris was not enlarged The blood pressure varied between 170/110 and 190/110 There were numerous petechial and ecchymotic spots over the skin of the body The tourniquet test was positive The blood count was normal as were the bleeding and coagulation times The fasting blood sugar level was within the normal range but the glucose tolerance test revealed a markedly decreased tolerance *since the blood sugar was 235 mgm* per cent four hours after the ingestion of 1 75 grams of glucose per kilogram of body weight The basal metabolic rate was −4 per cent The blood cholesterol was 525 mgm per cent The blood urea nitrogen was normal The urine showed a trace of albumin X ray examination of the skeleton revealed no evidence of osteoporosis The sella turcica was normal Perirenal insufflation revealed a large tumor above *the left kidney The patient* was operated upon

and a left adrenal carcinoma was removed Six weeks after operation she presented a remarkable change Her facial expression and appearance had changed entirely The puffiness was almost completely gone and the ecchymotic areas had entirely disappeared The blood pressure now varied between 114/70 and 135/85 The glucose tolerance curve tended to revert to the normal pattern During this six week period she had had one normal menstrual period

The second case was also that of a woman of thirty four who was well until three years before admission to the hospital The first change noted was that of a progressive obesity limited to the face neck and trunk while the extremities were spared There was a distinct change in her facial appearance due to the development of heavy jowls and hirsutism Soon thereafter she began to suffer from headache dyspnea on exertion polyuria and polydipsia

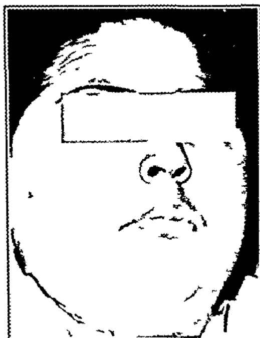


FIG 21 —A woman aged 28 years with Cushing s syndrome due to an adrenal cortical adenoma

Sugar was found in her urine Her head hair began to thin and she noted areas of ecchymoses which appeared spontaneously She gained 25 pounds in weight in one year She developed amenorrhea approximately two and one-half years after the onset of her illness The blood pressure before admission to the hospital was 160/110

When she was admitted to the hospital she presented the clinical features of Cushing s syndrome The obesity was limited to her face and torso The face was plethoric and full with considerable hirsutism There was a rather extensive acneform eruption over the face back and chest There were numerous ecchymotic areas in the skin Cutis marmorata was marked and numerous purplish abdominal striae were present The ocular fundi revealed the presence of thin arteries and retinal exudates The thyroid gland was slightly enlarged and nodular The heart was enlarged to the left There was kyphosis of the dorsal spine The blood pressure varied between 150/88

The patient was a female aged thirty-seven who was well until two and one-half years prior to admission to the hospital At the time of the onset of her illness she noticed a slight but definite decrease in visual acuity A year later she began to develop large ecchymotic areas over the lower extremities which recurred at frequent intervals Two years after the onset of her symptoms she noticed a change in the appearance of the face Her face became round puffy plethoric with coarsening of the features and marked hirsutism During this period of time she developed amenorrhea On physical examination she was found to be very obese but the obesity was limited essentially to the face neck shoulders and abdomen The upper and lower extremities were surprisingly thin She had many purplish striae over the abdomen and large ecchymotic areas over the lower extremities Pelvic examination failed to reveal any adnexal masses There was considerable enlargement of the clitoris however The blood pressure was 154/114 The blood hemoglobin was 105 per cent red blood cells 5 4 million The white blood cell count and differential were normal The oral glucose tolerance test employing 1 75 grams of glucose per kilogram of body weight yielded the following results Control 70 mgm per cent one-half hour 150 one hour 250 two hour 175 three hours 210 four hours 110 and five hour 65 mgm per cent The serum cholesterol was 230 calcium 8 8 and inorganic phosphorous 2 9 mgm per cent The blood phosphatase was 9 4 K A units The urine frequently showed trace of sugar X ray studies showed a normal sella marked osteoporosis of the entire spine and an old fracture of the left fifth rib in the anterior axillary line Perirenal insufflation revealed a mass on the left side above the kidney and on operation a left adrenal cortical tumor the size of a plum was removed

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normal glucose tolerance curve However in only 3 instances was the fasting blood sugar level elevated and in these 3 patients there was a fairly constant glycosuria In none of these 3 cases was the elevation of the fasting blood sugar level or the degree of glycosuria particularly pronounced Of interest is the recent case reported by Sprague in which the only manifestation of an adrenal cortical tumor was diabetes mellitus [145 146]

The hyperglycemia and glycosuria when they occur are difficult to control The disturbance in carbohydrate metabolism is not as readily responsive to insulin and dietary therapy as is the case of true diabetes Relatively large amounts of insulin and rigid dietary restrictions are necessary to produce even a moderate degree of regulation This is understandable in view of the nature of the disturbance However from the therapeutic point of view it is usually not necessary and not particularly desirable to attempt to regulate the disturbance in carbohydrate metabolism except in those instances in which the hyperglycemia and glycosuria are constant and marked Diabetic coma has not been observed in the untreated patients and even mild degrees of ketosis are uncommon With the successful removal of an adrenal cortical tumor the associated disturbances in carbohydrate metabolism disappear

The mechanism of the carbohydrate disturbance is probably dependent upon two factors The first is the relation of the adrenal cortex to protein catabolism and the second is the effect of various adrenal cortical hormones on the peripheral oxidation of glucose Under normal circumstances the adrenal cortex plays a role in the catabolism of proteins and their conversion into glucose and glycogen [101] It may be as suggested by the experiments of Wells and Kendall[107] that the adrenal cortex is concerned mostly with the breakdown of tissue into amino acids while it plays very little part in the deamination of amino acids and their subsequent conversion into glycogen In any event the first step is as critical as the second in glyconeogenesis The fasting adrenalectomized animal will continue to deposit glycogen in the liver and under the influence of phlorizin will excrete glucose in the urine in quantities parallel to the urinary nitrogen excretion only so long as adrenal cortical extract is administered This would suggest that in patients with adrenal cortical tumors or hyperplasia the increase in adrenal hormones thus produced would enhance the rate and extent of protein breakdown That such extensive tissue catabolism occurs in these patients was originally demonstrated by Woodyatt[1] and subsequently confirmed by Albright and his group [103] These investigators found negative nitrogen balances in patients manifesting Cushing's syndrome Such excessive tissue destruction eventually results in an increase in gluconeogenesis

In addition to the above factor the recent studies of Wells and Kendall [107] Ingle and Thorn [104] and Long[10] suggest that certain hormones of the adrenal cortex interfere with the utilization of glucose by the peripheral tissues Thus 11-dehydro 17 hydroxy-corticosterone (Compound E) when administered to an adrenalectomized pancreatectomized dog produces an increase in the glycosuria not accompanied by a parallel increase in the urinary nitrogen

and 175/115 The x ray of the sella turcica was normal Roentgenographic study of the skull vertebral column and ribs revealed extremely advanced decalcification with areas in the ribs suggestive of old healed spontaneous fractures The fasting blood sugar level was normal, but three hours after the ingestion of 50 grams of glucose the blood sugar level was 360 mgm per cent and 3 per cent glucose appeared in the urine The blood cholesterol was 320 mgm per cent The basal metabolic rate was −11 per cent The blood count was normal as were the bleeding and coagulation times The tourniquet test was positive Perirenal insufflation revealed the presence of a large mass above the right kidney and at operation an encapsulated right adrenal tumor the size of a walnut was removed

These three cases represent fairly typical examples of the adrenogenital syndrome with Cushing's syndrome due to a tumor of the adrenal cortex The disease, when it is fully manifest presents a striking clinical picture that is not easily forgotten The metabolic abnormalities vary in degree in different patients, and are by no means always present but some of them such as the disturbance in carbohydrate metabolism the osteoporosis the hypertension, abdominal striae and the petechiae and ecchymoses are evident in most instances



Fig 22 —Patient in figure 21 six months following successful removal of an adrenal cortical adenoma

Disturbances in Carbohydrate Metabolism —In view of the relationship of the adrenal cortex to carbohydrate metabolism one would expect some disturbance in carbohydrate metabolism to be present always This is not entirely true and as a matter of fact frank diabetes has occurred relatively infrequently Lukens and his group[49] analyzed 55 cases of adrenal cortical tumor and hyperplasia and found no evidence of impairment of carbohydrate metabolism in 28 instances Of the remaining 27 patients 19 showed a marked glycosuria and 8 manifested only deficient carbohydrate utilization as measured by the dextrose tolerance curve Kepler and Wilder[99] in 8 patients with adrenal cortical tumor found definite diabetes in only 1 instance and some evidence of abnormal carbohydrate metabolism in 4 others Shepardson and Shapiro[100] in analyzing the literature found only 18 instances of adrenal cortical tumor associated with diabetes In 10 patients carefully observed in our own clinic all but 1 showed an ab

spine with compression fractures of the 6th 8th and 9th dorsal and 1st lumbar vertebrae There was in addition a transverse fracture through the left 7th rib in its axillary portion

The osteoporotic changes in the spine when extensive enough produce a marked radiolucent quality in the vertebral bodies due to a uniform decrease in the number and density of the trabeculæ Actually however these changes are not significantly characteristic to differentiate them for osteoporosis of the spine due to any other cause

Sussman and Copelman[10] describe the occasional appearance of certain changes in the ribs which they feel are pathognomonic of Cushing's syndrome These characteristic changes however are by no means always present The finding is characterized by a peculiar appearance of the anterior ends of the lower ribs just lateral to the costochondral junction



FIG 23 —Adrenal cortical tumor with collapse of 3rd and 4th dorsal vertebræ

The rib is expanded to about twice its normal size for a distance of an inch and is homogeneously increased in density These areas are much more dense than the surrounding bone and suggest callus formation associated with healed fractures

The mechanism through which osteoporosis develops in this disease is still obscure The initial suspicion would be that the parathyroids are secondarily involved as a result of the disorder of the adrenals or pituitary Indeed several instances are recorded in which tumors of the parathyroid glands have been found in association with Cushing's syndrome[56, 108, 109, 110] In addition in the early stages of the disease hypercalcinuria is occasionally observed with the patient in negative calcium balance[111, 11] and even the

These factors would explain the abnormalities in carbohydrate metabolism observed in patients with Cushing's syndrome and their refractoriness to the usual antidiabetic therapeutic measures. Of what significance is the restriction in carbohydrate intake in view of the constant and excessive endogenous source of carbohydrate formation? Similarly, the effect of insulin on the utilization of carbohydrates is mitigated, probably to a considerable extent, by the action of the adrenal cortical hormones on the peripheral oxidation of carbohydrates.

Osteoporosis in Adrenal Cortical Hyperfunction.—Osteoporosis occurs in the majority of patients with Cushing's syndrome. It was originally thought that the presence of decalcification was evidence of an absence of an adrenal cortical tumor and pointed to primary pituitary disease. With the accumulation of more clinical material it became evident that such bony changes occurred as frequently in those instances of Cushing's syndrome associated with primary adrenal disease as it did in those cases where the disease was ostensibly primarily pituitary in origin. The distinction then between pituitary basophilism and adrenal cortical tumor on this basis is impossible.

Eisenhardt and Thompson[106] in a review of the literature found that of 61 cases of Cushing's syndrome 53 had definite osteoporosis, 5 showed questionable changes, and in 3 instances the bones were perfectly normal. In 10 cases of Cushing's syndrome due to adrenal cortical tumor observed in our clinic, 9 had varying degrees of osteoporosis. The degree of decalcification may vary from a mild osteoporosis to one where the decalcification is extensive and marked and associated with the presence of spontaneous fractures. The decalcifying process may involve the skull, ribs, spine, and less frequently the long bones. When present in the skull it is usually irregularly distributed but generally involves the frontal and parietal bones. Sussman and Copelman[107] describe these areas in the skull as being triangular or ameboid in shape, with ill-defined margins. Occasionally they are roughly circular and may resemble areas of carcinomatous metastasis.

The osteoporosis of the spine usually involves all the vertebrae and may be extensive enough to produce a kyphosis of the dorsal spine or actual compression fractures. The following case exemplifies such an instance.

The patient was a thirty-three year old woman who had developed amenorrhea ten months before admission to the hospital. During this period of time she had noticed marked facial hirsutism, swelling, redness, and roundness of the face, and an acneform rash over the back. She had gained 12 pounds in weight. The physical examination revealed a short, obese, plethoric looking woman with a marked dorsal kyphosis. There were deep reddish striae over the left flank and the fingers and toes showed some acrocyanosis. The blood pressure was 160/100, hemoglobin was 100 per cent, red blood cells 5.2 million per c mm, and the urine was negative for sugar and Bence-Jones protein. A glucose tolerance test yielded the following results: Control 95 mgm per cent, one-half hour 185, one hour 200, two hours 180, three hours 160 mgm per cent. The serum cholesterol was 370 mgm per cent, the serum calcium was 10.0 and inorganic phosphorous 3.5 mgm per cent. The blood phosphatase was 20 K-A units. The blood urea nitrogen was 21 mgm per cent. The basal metabolic rate was −16 per cent. Roentgenologic studies showed slight generalized decalcification of the skull and long bones. The sella turcica was normal. There was extensive decalcification of the entire

icteristic of the latter A further difference between the two diseases is the almost complete absence of any reparative process in Cushing s syndrome while some new bone formation however meager does take place in the osteoporotic areas produced by parathyroid tumors Albright[112] speaks of the osteoporosis of Cushing s syndrome as due to a lack of bone matrix resulting from decreased activity of osteoblasts and due primarily to a disorder of protein metabolism

In the light of what we know about the physiology of the parathyroid glands and the characteristic metabolic changes observed in disorders of these bodies one must conclude that these glands are not particularly involved in the osteoporotic process in Cushing s syndrome Iversberg and Newburgh[113] have shown that there is a failure to absorb sufficient calcium and phosphorus in Cushing s syndrome to permit adequate retention of these ions In this event it is not unlikely that calcium and phosphorus may be withdrawn from the bones to make up for this lack

Recent evidence would tend to throw some light on the mechanisms involved in this type of osteoporosis The administration of adrenocorticotropin will result in the failure of wounds to heal Under the influence of the secretion of the adrenal cortex secondary to the injection of adrenocorticotropin the laying down of ground substance and connective tissue is inhibited In addition we have shown in our laboratory that in a case of Cushing s syndrome due to adrenal cortical hyperplasia the administration of adrenocorticotropin induced a markedly negative calcium phosphorus and to a lesser extent nitrogen balance The excessive loss of calcium was almost entirely via the feces The depletion of the bony protein matrix and the negative calcium balance probably account for the osteoporosis seen in Cushing s syndrome Following the therapeutic administration of ACTH or cortisone in other diseases the osteoporosis which develops may occasionally be so severe as to result in pathological fracture

Hypertension in Adrenal Cortical Hyperfunction —Hypertension is observed in most instances of adrenal cortical tumor or hyperplasia with Cushing s syndrome The hypertension may be relatively mild or may attain excessive and alarming levels There occurs a proportionate increase in both the systolic and the diastolic levels When the elevation in blood pressure has persisted for a considerable time secondary severe renal and cardiac changes supervene In that event the associated phenomena are no different from those observed in the usual severe hypertensive cardiovascular disease Narrowing and nicking of the retinal blood vessels as well as exudates and hemorrhages are observed in the fundi Renal and cardiac failure as well as cerebral vascular accidents may occur and death due to these causes in this disease is not uncommon Such a case was observed in our clinic and previously reported by Oppenheimer and Silver[20]

The patient was a thirty seven old married woman who was well until 1934 when her left ovary and tube were removed Shortly after pronounced facial hirsutism appeared and she began to gain weight rapidly She became dyspneic developed ankle edema and was told that she had hypertension Approximately one and one-half years after the onset of her symptoms she developed amenorrhea which persisted throughout the subsequent course of her illness On physical examination she manifested the typical appearance

occurrence of nephrolithiasis is not too uncommon.[11] In the large majority of instances, however, there are no overt abnormalities of the parathyroid either grossly or histologically. The calcium balance studies are in general quite normal[103] and this is true of the blood calcium and phosphorous levels. The blood phosphatase is not elevated in the early stages of the

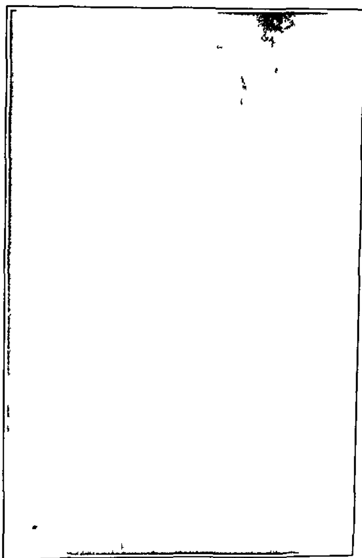


Fig 24 — Moderate osteoporosis of the femur in a patient with an adrenal cortical tumor with Cushing's syndrome

illness, but later tends to increase. However, the blood phosphatase never attains the values observed in patients with true osteitis fibrosa cystica. The histology of the bony changes observed in Cushing's syndrome is quite different from that seen in parathyroid tumor in that the former never manifests the cystic changes and giant cell tumors so char

The elevation in blood pressure obtained with desoxycorticosterone acetate is independent of the retention of sodium ion or of an increase in the circulating blood volume.[122, 124] It would appear to be a highly specific effect of this steroid compound. Grollman and his coworkers[113] have suggested that the hypertensive effect of desoxycorticosterone may be due to the toxic action of steroids on the kidneys. However, there is no convincing evidence to support this contention. Selye and Hall[1] have succeeded in producing renal changes in fowl and mammals with desoxycorticosterone similar to those seen in nephrosclerosis. This may be the manner in which the hypertension is produced. However, it is a moot point as to whether the renal changes observed under the experimental conditions may not be due to the hypertension rather than to the drug. Similar renal changes have not been noted in patients with Addison's disease who had been treated during life with desoxycorticosterone. It may be as Rodbard and and Freed[1 3] have suggested that desoxycorticosterone exercises a direct effect on the smooth musculature of the arterioles. Or perhaps it plays some part on the metabolism of the kidney and thus effects the production of the renal hypertensive factor. Certain evidence has accumulated to support the contention that the adrenals are essential for the potentiation of the action of rennin.[1 6 1 7] This aspect of the discussion, however, is at present highly speculative. The fact is that desoxycorticosterone has a specific blood pressure raising effect. Essentially the same is true of cortisone and of ACTH, both of which are capable of producing hypertension, the latter however only in the presence of intact adrenals.

The experimental data would suggest that the hypertension observed in patients with Cushing's syndrome is due to the excessive production by the adrenal cortex of a hypertensive factor. The extensive vascular changes subsequently observed are most likely due to the persistent and marked elevation of the blood pressure. In this respect these patients behave no differently than do those with essential hypertension who after many years begin to develop overt evidences of vascular, renal, and cardiac damage.

Ecchymoses, Purpura and Striæ.—Patients with Cushing's syndrome tend to develop ecchymosis, purpura, and petechiæ. These manifestations are not due to any intrinsic blood dyscrasia, since the bleeding and coagulation times as well as the clot retractility, prothrombin index, and platelet counts are essentially normal. The tourniquet test is usually positive, and this phenomenon was observed in 6 of our 10 patients. These patients usually have a thin skin and a marked tendency to easy bruisability. This may be due to the reduction in protein tissue mass which occurs during the progress of the disease[11] and it may be that the ecchymoses are due to this factor. However, such subcutaneous bleeding frequently occurs spontaneously without preceding trauma. It is realized that the adrenal cortex plays a considerable part in capillary permeability. However, it is only in adrenal insufficiency that there occurs an increase in capillary permeability[128] and hence one would hardly expect this phenomenon in Cushing's syndrome, which represents the antithesis of adrenal cortical insufficiency.

Freed and Lindner[1 9] presented an interesting report which sheds additional light on the relation of the adrenal cortical steroids to capillary permeability. Although whole adrenal cortical extract and crystalline

of Cushing's syndrome The face was puffy and plethoric There was a generalized hirsutism, and many purplish striae were noted over the abdominal wall The obesity was limited essentially to the face neck and torso while the arms and legs remained thin The eye grounds presented the usual features of hypertensive neuroretinitis with hemorrhages exudates and peripapillary edema The blood pressure varied between 195/130 and 205/140 The blood urea nitrogen was 58 mgm per cent The fasting blood sugar level varied between 135 and 220 mgm *per cent* *The basal metabolic rate was + 12 per cent* *The patient developed signs of cardiac decompensation and despite the usual therapeutic measures died of congestive heart failure*

Mainzer[9] reports the case of an eight and one half year old child with Cushing's syndrome who died of a cerebral vascular accident as a result of a severe and prolonged hypertension Unlike that observed in instances of pheochromocytoma and paraganglioma the hypertension in Cushing's syndrome is not paroxysmal in character but is continuous and tends to increase in severity unless the underlying disease is successfully treated The removal of the adrenal tumor is followed by a reduction in the blood pressure to normal levels even in those instances in which retinal vascular changes are already evident

The cause for the hypertension in these patients is by no means clear However enough experimental data concerning the effect of various adrenal steroid fractions on the blood pressure is available to enable us to speculate profitably about the mechanism involved It is interesting that potent whole adrenal cortical extract administered in large doses is incapable of causing an abnormal elevation of the blood pressure in the normal or adrenalectomized animal or in the normal individual or the patient with Addison's disease[113] This is in contrast to the results obtained with the use of desoxycorticosterone acetate It is a matter of clinical observation that patients with Addison's disease treated with this compound tend to develop hypertension the blood pressure sometimes attaining alarming levels[114,115,116,117,118,119,120] Similar results have been obtained following the experimental use of this steroid compound in normal non adrenalectomized animals and in patients with no evidence of adrenal cortical disease[113,121,122,123,124] It is interesting however that the blood pressure raising effect of desoxycorticosterone is less consistent and less striking in the normal animal than it is in the bilaterally adrenalectomized one[122] In our own experience essentially the same is true in normal individuals in contrast to that observed in patients with destruction of the adrenal cortex Although hypertensive effects are obtained in the former group they are less easily elicited than in the latter patients This may bear some relationship to the fact that whole adrenal cortical extract which is in reality a combination of several adrenal cortical fractions is incapable of producing an elevation of the blood pressure above normal levels It would suggest that in addition to the hypertensive factor manufactured by the adrenal cortex an additional blood pressure balancing fraction is similarly produced In patients whose adrenals are completely destroyed as in Addison's disease *this factor* is *not normally formed* and the increase blood pressure with desoxycorticosterone is therefore more readily obtained

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corticosterone decrease the permeability of the skin capillaries as evidenced by their neutralizing effect on 'leukotaxin'[130] this is apparently *not true* as concerns the effect of desoxycorticosterone[129] This latter compound not only fails to neutralize the effect of leukotaxin, but produces some increase in capillary permeability In the light of these observations, it is at least possible that the easy bruisability the tendency to ecchymoses and purpura, may be due both to a reduction in tissue mass which reduces the protective support of the skin capillaries and to an increase in permeability of the latter

The *striæ atrophicæ* represent a consistent phenomenon observed in patients with adrenal tumor with Cushing's syndrome These striæ are usually present over the lower abdomen generally in the flanks on the buttocks the upper part of the thighs and arms and frequently extend along the outer aspects of the breast They are usually violaceous in color and run roughly parallel Such striæ are not infrequently observed in normal stout individuals but they are generally colorless in this group However the presence of purplish striæ is by no means pathognomonic of Cushing's syndrome In the latter group of patients the striæ generally appear over the obese areas in which the skin is distended although they have apparently been observed in patients in whom this factor does not operate[131] Albright and his coworkers[103] have suggested that the striæ are due to a thinning of the skin due to protein depletion

Miscellaneous Abnormalities Observed in Patients with Adrenal Cortical Tumors with Cushing's Syndrome —These patients frequently develop *skin infections* the most common of which is an acneform eruption over the face upper part of the chest back and buttocks There is nothing particularly characteristic of this eruption except the frequency of appearance in this group Occasionally the acne will be the first symptom observed and may antedate the appearance of the other and more striking symptoms by a considerable period of time It is probable that the susceptibility of the skin to these infections is an evidence of virilization

Marked diurnal and nocturnal urinary frequency has been noted often This is usually associated with a corresponding polydipsia It is seen in those instances in which there is hyperglycemia and glycosuria and the latter probably accounts at least in part for the urinary frequency However it is just as commonly observed in those patients who manifest neither an elevation in the blood sugar level nor glycosuria As previously mentioned patients with Cushing's syndrome frequently show a marked urinary nitrogen excretion and the polyuria is related to this phenomenon too The urinary frequency then is an expression of glycosuria or excessive urinary nitrogen excretion or both

Polycythemia and acrocyanosis are less commonly observed phenomena The polycythemia is generally moderate in degree and the red blood cell count rarely exceeds 6 million per cubic millimeter In our group of 10 patients the highest count observed was 6 25 million noted in only one instance In the remaining 9 patients the red blood cell count varied from 4 5 to 5 3 million per c mm and the hemoglobin from 78 to 110 per cent Moehlig and Bates[13] however describe the case of a man with a large adrenal tumor whose only evidence of the disease was a red blood cell count of 8,194,000 with a hemoglobin of 153 per cent In addition to the adrenal

cortical tumor this patient showed marked hyperplasia of the basophil cells of the pituitary These authors concluded that the erythremia was due to a disturbance in pituitary function It is interesting that the erythrocytosis observed in these patients is not associated with an increase in blood volume

There is usually a leukocytosis a lymphocytopenia and eosinopenia in patients with Cushing s syndrome [146] A reduction in the plasma albumin as well as in the gamma globulin fractions has been described [147]

The skin assumes a *diffuse dusky hue* Often the skin of the entire body becomes mottled in appearance similar to that observed in cutis marmorata Generally the duskiness and mottled appearance are limited to the extremities and to a somewhat lesser extent to the face The lips and nail beds assume a dark cyanotic hue The dusky appearance of the skin is not related to any corresponding increase in the peripheral red blood cell count since the latter is rarely sufficiently elevated to produce such a phenomenon Rather it is due to some diffuse vascular change which occurs in association with this illness That the dusky coloring is not a true cyanosis is shown by the fact that no alteration in the oxygenation of the red blood cells has been observed

Fatigue and muscular weakness to varying degree are frequently observed These symptoms are usually moderate but occasionally the asthenia may be profound Such a case was reported by Farber and his coworkers [81] and is described elsewhere in this chapter p 321 Beginning with fatigue evidenced on relatively mild exertion this symptom progressed to the point where the muscular weakness was so marked as to render even the slightest effort almost impossible The muscular weakness is probably due to the reduction in muscle mass as evidenced both by the low creatinine excretion[11] and by the excessive urinary nitrogen excretion A further contributory factor may be the depletion of intracellular Potassium The extensive muscular destruction must be due to the hypergluconeogenesis which occurs in the presence of hyperfunction of the adrenal cortex and which is associated with a breakdown of tissue into amino acids

Many of the patients with adrenal cortical tumors manifest *mental and emotional* changes to varying degrees In occasional instances these alterations are profound and disturbing enough to suggest the more serious psychoses Whether these personality difficulties are a primary manifestation of the disease or whether they are secondary to the startling changes in the physical appearance of the patient it is impossible to say Certainly the cosmetic changes which occur are disturbing enough to constitute severe psychic trauma Nevertheless some of the emotional dislocations must constitute expressions of abnormal endocrine function This is so frequently evidenced by the change in sexual interest manifested by the patient Many of the women thus afflicted lost interest in any male contacts and an occasional one will show definite homosexual trends It is indeed surprising that such overt homosexuality is not manifested more often It is interesting that with the successful removal of the adrenal tumor the sexual aberrations disappear fairly promptly with a return to the original pattern Such a case was described by Gordon Holmes [13]

corticosterone decrease the permeability of the skin capillaries as evidenced by their neutralizing effect on leukotaxin[130] this is apparently not true as concerns the effect of desoxycorticosterone[1 9] This latter compound not only fails to neutralize the effect of 'leukotaxin' but produces some increase in capillary permeability In the light of these observations it is at least possible that the easy bruisability, the tendency to ecchymoses and purpura may be due both to a reduction in tissue mass which reduces the protective support of the skin capillaries and to an increase in permeability of the latter

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that is the changes in the physical appearance—or whether it is due to the primary endocrine dysfunction the general character of which is common to all these patients is a matter for speculation

Adrenal Cortical Tumors in Adult Males.—Hormonal adrenal cortical tumors in males are extremely rare When they occur they may assume one of two forms Either they present the picture of a Cushing's syndrome without virilism or they show actual signs of feminization with very few manifestations of the Cushing counterpart Even in those instances in which feminization is not predominant there occurs a loss of libido and a decrease in the size of the genitals

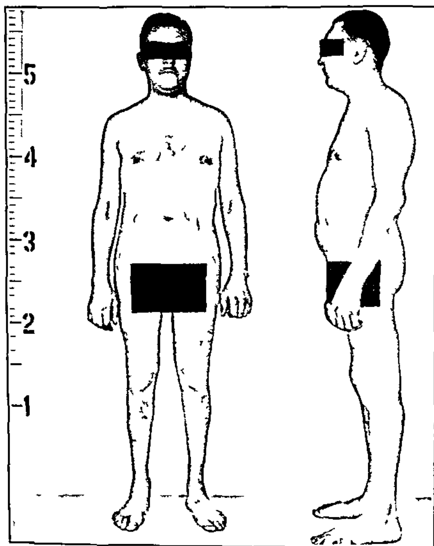


Fig 25.—Patient with Cushing's syndrome due to an adrenal cortical tumor Note buffalo-like fascies and characteristic striæ

This was a young women of twenty three with all the signs and symptoms associated with an adrenal cortical tumor Prior to the onset of the illness she had been fond of male society engaged in the usual flirtations, and was moderately amorous During the period of her illness there was a complete loss of interest in men and a decided and overt preference for the society of women After the successful removal of the tumor she again became interested in male showed signs of a highly erotic temperament and maintained a completely normal relationship with women

These sexual changes when present manifest themselves with the disappearance of the menses and when reversion to a normal pattern occurs following successful therapy it is always preceded by the return of the catamenia

Other than the sexual dislocations the patients frequently manifest *severe depression* occasionally *mania and excitement* and *periods of paranoid confusion* They are frequently preoccupied with *thoughts of suicide* which constitutes no idle threat and require careful watching However depression is most commonly noted and almost all patients with adrenal tumors develop this symptom to varying degrees *Irritability* is not infrequently observed and the quarrelsome tendencies may constitute a ward problem These manifestations are well exemplified in the instance of a patient observed in our group

This is a young woman of twenty five who had been perfectly well until six months before admission to the hospital in the spring of 1944 During this period of six months she had noticed vague pains in the calves of the legs and the lower part of the back She had developed marked urinary frequency both diurnal and nocturnal Her husband commented upon the fact that her personality had undergone marked changes She had become irritable and quarrelsome the ill humors frequently reached manic proportions and alternated with prolonged periods of severe depression She had become forgetful and slovenly and regarded most of her associates with suspicion There had been a gain of 20 pounds in weight and the contours of her face had become rounded There were pads of fat over the upper back and shoulders while no change apparently occurred in the extremities Two months prior to admission to the hospital hirsutism appeared on the face and eventually on the extremities and arms There had been no change in the menses which occurred with the usual regularity When seen in the hospital she presented the characteristic features of Cushing's syndrome including hypertension osteoporosis abdominal striæ and a diabetic Janney curve In addition she was quarrelsome and uncooperative She manifested marked persecutory trends and regarded the other occupants of the ward and the medical attendants with hostile suspicion She had periods of depression during which she would neither eat nor talk Quite suddenly the depression would lift and be followed by a phase of relative excitement On several occasions she threatened suicide although no actual attempt was ever made After the successful removal of an adenoma of the right adrenal there occurred a gradual recession of both the physical and mental symptoms Six months after the operation she presented the appearance of a rather attractive perfectly normal young woman She was pleasant and agreeable spoke intelligently and quietly and had lost the suspicious attitude so characteristic of her during her illness Her social relationships had assumed the pattern present prior to the onset of the disease She again had many friends with whom she apparently got along well

It is noteworthy that the mental changes when present are in general similar in all patients with adrenal cortical tumor Whether this is due to the fact that the secondary exciting trauma is identical in all instances—

palpable and there was a feeling of resistance or a mass above and to its inner side X ray examinations showed an ill defined upper pole of the left kidney with a rounded shadow impinging Pyelography disclosed normal pelves on both sides the left kidney appeared to be pushed down with a rounded shadow superimposed upon its upper outline The Wassermann reaction was negative the sedimentation rate was raised to 14 mm per hour blood urea was 39 mgm per cent A blood examination showed the hemoglobin to be 80 per cent erythrocytes 4 600 000 leucocytes 7400 with 46 per cent polymorphs and 49 per cent lymphocytes In July 1934 a large malignant tumor of the left adrenal was removed Convalescence was somewhat protracted After two months he began to gain weight and strength the breasts became smaller and the genitals larger There was some return of sexual urge and potency but no approach to normality Course of deep x ray therapy were started in October 1934 and continued intermittently In March 1935 the pain below the left scapula recurred and radiated along the costal margin The patient looked plethoric the breasts were full and the genitals rather small The abdomen was adipose and lineæ distensæ which had appeared early in the illness were well marked The blood pressure was 120/80 Sexual desire had again declined and coitus was achieved with difficulty The hair on the trunk was very profuse and whereas this had always been so the patient thought it had increased with the onset of the illness On the other hand the beard growth was if anything less strong than previously The weight continued to increase up to June 1935 when it reached 156 pounds but from this time onwards there was a progressive fall Impotence became complete and the breasts grew larger at first and then smaller with the general loss of fat During the next six months there was a progressive decline in the patient s condition and in April 1936 a laparotomy showed metastatic growth in the liver and a fibrous mass at the original site of the tumor The patient died in June 1936

During the course of the illness this patient excreted an excess of estrogenic hormone in the urine prior to operation The excess disappeared after surgical removal of the tumor and recession of the signs of feminization but recurred again with metastasis and return of the feminizing process The Ascheim Zondek test was negative on the two occasions in which it was performed after the metastasis was evidenced

The remaining cases recorded in the literature presented essentially the same clinical picture In Bittorf s case [135] which is the first instance of feminization recorded there was enlargement of the breasts decrease in size of the testes and impotence At autopsy a malignant adrenal tumor was found The testes were extremely small while the breasts consisted of loose connective tissue and true mammary glandular tissue Zum Busch s patient[136] had painless swelling of both breasts with enlargement of the nipples from which a milky fluid could be expressed At necropsy a malignant left adrenal cortical tumor was found which had metastasized extensively to the lungs pleura and mesenteric nodes In Lisser s patient [137] too there was enlargement of the breasts from which a thin watery secretion could be expressed This patient had an adrenal cortical carcinoma with pulmonary metastasis The tumor had apparently arisen from a retroperitoneal adrenal rest Holl[138] reported 2 instances of feminization

The first was a boy of fifteen whose breasts were considerably enlarged and projected like those of a girl The nipples were darkly pigmented and the supra pubic hair was feminine in distribution At operation a malignant adrenal cortical tumor was found

Nolini and O'Brien[133] describe the case of a man of thirty six whose first complaint was the appearance of reddish striæ on the right side of the abdomen. He then noticed a tendency to a rapid gain in weight with the distribution of the obesity limited to the back of the neck, shoulders and girdle. His face became rounded and plethoric, while the hair on his face and extremities tended to decrease somewhat in amount. More striæ appeared on the abdomen. He noticed weakness, loss of libido, and rather severe pains in the back. The testes had decreased in size, the blood pressure was 205/140, the hemoglobin was 102 per cent, while the red blood cell count was 5 090 000. The glucose tolerance was decreased. At autopsy a malignant right adrenal tumor was found.

A similar case was observed in our clinic.

The patient was a man of twenty seven. In 1941 he noticed a rapid gain in weight, swelling and redness of the face, thinning of the hair, polyuria, polydypsia, diminution in the size of the penis, and loss of libido. On physical examination he was found to be an obese man with florid buffalo-like face and marked purplish axillary and abdominal striæ. The blood pressure was 178/104. The blood hemoglobin was 91 per cent with 4.4 million red blood cells per c mm. The white blood cell count and differential study were normal. The urine showed a 4 plus sugar. The blood urea nitrogen was 11 mgm per cent, and the blood sugar 200 mgm per cent. The serum cholesterol was 440, esterified cholesterol 225, calcium 10.1, inorganic phosphorous 2.7 mgm per cent, and chlorides 100 m eq per liter. The blood phosphatase was 19 K A units. The glucose tolerance curve was typically diabetic in character with a two-hour rise to 410 mgm per cent. The basal metabolic rate was −31 per cent. The visual fields showed slight temporal constriction of the peripheral fields. X ray of the skull and long bones was normal, but the lumbosacral spine showed moderate generalized osteoporosis with compression of several of the vertebral bodies. Perirenal insufflation failed to reveal any adrenal masses, but at a subsequent exploratory operation a right adrenal cortical tumor was found.

Both these cases are fairly typical of adrenal cortical tumors in males. The predominant picture is that of the metabolic disturbances of Cushing's syndrome. There are no evidences of virilization, but rather some decrease in the size of the genitals and reduction in libido.

The counterpart of the masculinization observed in women is the marked feminization sometimes seen in the men with adrenal tumors. Approximately 11 such instances of feminization have been described.[11] The case reported by Simpson and Joll[134] bears repetition.

The patient was a physician aged thirty four, with one child. He was in good health until November 1933, when pain below the left scapula began. This was noticed on waking in the morning, recurred at odd times throughout the day and lasted some minutes or hours, but was unrelated to food or exertion. After a barium meal radiography showed a small gastric ulcer, alkaline treatment with diet was given for some months without relief. At this time it would appear that the pain, together with a vague dyspepsia and lassitude, were the presenting features, but on taking the history in retrospect a year later the following points emerged. In 1932 the breasts began to enlarge, and in August 1933 there was loss of libido and partial impotence. Erection of the penis and coitus were achieved with difficulty, and the genital organ had become smaller. There were also big fluctuations in weight. Whereas the normal weight up to 1932 was 154 pounds, in the next twelve months there was a rapid gain up to 182 pounds, and then a still more rapid fall to 126 pounds in August 1934. On physical examination the patient looked ill. The blood pressure was 116/70, pulse 70 ... the left kidney was low and easily

palpable and there was a feeling of resistance or a mass above and to its inner side X ray examinations showed an ill-defined upper pole of the left kidney with a rounded shadow impinging Pyelography disclosed normal pelves on both sides the left kidney appeared to be pushed down with a rounded shadow superimposed upon its upper outline The Wassermann reaction was negative the sedimentation rate was raised to 14 mm per hour blood urea was 39 mgm per cent A blood examination showed the hemoglobin to be 80 per cent erythrocytes 4 600 000 leucocytes 7400 with 46 per cent polymorphs and 49 per cent lymphocytes In July 1934 a large malignant tumor of the left adrenal was removed Convalescence was somewhat protracted After two months he began to gain weight and strength the breast became smaller and the genitals larger There was some return of sexual urge and potency but no approach to normality Courses of deep x ray therapy were started in October 1934 and continued intermittently In March 1935 the pain below the left scapula recurred and radiated along the costal margin The patient looked plethoric the breasts were full and the genitals rather small The abdomen was adipose and linear distension which had appeared early in the illness were well marked The blood pressure was 120/80 Sexual desire had again declined and coitus was achieved with difficulty The hair on the trunk was very profuse and whereas this had always been so the patient thought it had increased with the onset of the illness On the other hand the beard growth was if anything less strong than previously The weight continued to increase up to June 1935 when it reached 156 pound but from this time onwards there was a progressive fall Impotence became complete and the breasts grew larger at first and then smaller with the general loss of fat During the next six months there was a progressive decline in the patient s condition and in April 1936 a laparotomy showed metastatic growth in the liver and a fibrous mass at the original site of the tumor The patient died in June 1936

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The second case recorded by Holl is of particular interest in that there occurred a complete recession of the signs of feminization with the successful removal of the tumor

The patient was a man of forty four married with two children His sexual function had been perfectly normal until the onset of the illness In the spring of 1927 *both breasts enlarged became painful and in appearance resembled* female breasts The nipples were large and pigmented and veins developed over the mamma The testes and penis became smaller libido was lost and sexual intercourse ceased In July 1929 a malignant adrenal cortical tumor *was removed One week after the operation the breasts became less sensitive* and one month later penile erection and ejaculations occurred and within several months there was a return to normal libido and sexual intercourse Six months after operation the patient appeared to be quite normal The breasts and nipples were small and insensitive while the penis and the testes had grown to normal dimensions There was a reduction in adiposity, and the facies had lost their feminine appearance

Glass and Bergman[139] report 2 instances of genital atrophy and enlargement *of the breasts which they refer to as subclinical adrenogenital* syndrome These cases were apparently not associated with an adrenal cortical tumor but the partial feminization was ascribed to hyperfunction of the adrenal cortex

The recorded definite cases of feminizing syndrome in the adult male have two significant observations in common In all instances the adrenal cortical tumor was malignant in character and all of the patients showed a paucity of the metabolic disturbances so characteristic of Cushing s syndrome This is in marked contrast to the masculinizing syndrome seen in the female Such a syndrome in the female can be produced by a variety of causes including benign or malignant tumors of the adrenal cortex adrenal cortical hyperplasia and as previously emphasized the syndrome has been observed in instances where no gross pathologic changes have been noted This is not to say that these enumerated factors may not conceivably produce feminization in the male such as possibly the cases reported by Glass and Bergman Nevertheless of the cases reported to date all have shown the presence of malignant adrenal cortical tumors

Equally interesting is the fact that the male patients with marked feminization showed few evidences of the Cushing syndrome None had hypertension osteoporosis or disturbances in carbohydrate metabolism Some were obese and plethoric and a few had the characteristic purplish striae

This relatively sharp division of clinical types in the adult male in which a Cushing s syndrome is predominantly present and where the pathologic change may be present in the pituitary adrenal or thymus—and the marked feminizing type where the signs of Cushing s syndrome are meager and where the pathology at least of the proven recorded cases has been an adrenal cortical carcinoma is not quite so true of women The latter may present masculinization alone or a combination of virilism and Cushing s syndrome As far as can be determined histologically there seem to be no differences in the structure of the tumor to account for the various clinical pictures produced

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Chapter 12

BLOOD ELECTROLYTE AND HORMONAL STUDIES

Diagnosis, Prognosis and Treatment of Adrenal Cortical Tumors and Hyperplasia

Blood Electrolyte Changes in Patients with Hyperfunction of the Adrenal Cortex.—In view of the relationship of the adrenal cortex to electrolyte metabolism, notably that of sodium, chloride and potassium, one might anticipate that some alterations in the values of these ions might be encountered in patients with cortical hyperfunction. Destruction of the adrenal cortex such as occurs in Addison's disease is associated with an increase in the urinary excretion of sodium and chloride, a retention of potassium, and a consequent reduction in blood sodium, chloride and CO_2 values, and an elevation of the blood potassium level. Since adrenal cortical hyperfunction represents in a sense the direct antithesis of Addison's disease, one is led to expect corresponding changes in the urine and blood electrolyte values. It is indeed interesting and perhaps significant that such changes occur infrequently.

Loeb studied the blood sodium, potassium, and chloride levels and the urinary excretion of these ions in several instances of the adrenogenital and Cushing's syndrome cases reported by Cahill and his group[1] and and found no deviations from the normal. Wilson, Power and Kepler in a series of more than 30 cases of Cushing's syndrome, 13 of which were due to adrenal cortical tumors, found only 3 cases in which there were marked changes in the electrolyte pattern of the blood. In 8 cases of our group of proven adrenal cortical tumors with Cushing's syndrome, significant alterations in the blood sodium, chloride or potassium levels were noted in 3 instances. Anderson, Haymaker and Joseph[3] found the serum potassium level to be at the lower limits of normal while the blood sodium values were at the upper limits normal in 3 cases with Cushing's syndrome. In these same patients there was a reduction in the urinary excretion of sodium and an elevation in the potassium excretion. Reports of variations in the blood electrolyte levels have been recorded in individual cases by McQuarrie, Johnson and Ziegler[4] and by Goldzieher.[5]

It is unfortunate that so few electrolyte studies have been reported in such cases. Of 45 fairly well-defined cases of Cushing's syndrome collected from the literature and including our own group in which blood sodium, chloride and potassium levels were determined, some abnormalities in the sodium ion values were found in 7 instances, in chloride levels in 5, and in potassium levels in 11 instances. (*See* Tables 17 and 18, page 350.)

What is the nature of the electrolyte disturbances observed? In 1933 Kepler[6] reported the occurrence of a reduction in the blood level of chlorides and potassium, a considerable elevation in the blood CO_2, and a normal

concentration of blood sodium. Subsequently 2 other such cases were reported by the Mayo Clinic group.[2,7] The case reported by McQuarrie and his group[4] also demonstrated considerable alkalosis, reduction in blood chlorides and potassium, but in this instance there was a marked elevation in the blood sodium level. Goldzieher's case[5] showed a high blood sodium and a reduction in blood potassium levels. In our own group of patients 1 showed results identical with those observed by McQuarrie. There was a moderate alkalosis with a reduction in the blood chlorides and potassium and a considerable elevation of the blood sodium. In another instance there was an elevation of blood sodium, reduction in blood potassium, but no alteration either in the CO_2 content of the blood or in the chlorides. In a third instance the only electrolyte abnormality observed was a reduction in the blood potassium value.

Table 17.—45 Collected Cases from the Literature in Which Blood Electrolyte Levels were Recorded

	Normal	*Elevated*	*Reduced*	*Questionable Elevation*	*Questionable Reduction*
Na	38	4	0	3	
Cl	40	0	5		
K	35	0	8		3

Table 18

Patient	*Blood Sodium meq/l*	*Blood Chloride meq/l*	*Blood Potassium meq/l*
A. R.	141	98	2.53
T. S.	140	102	4.0
M. A.	135.9	100	5.0
R. F.	137.4		
J. I.	137.7	106	4.2
R. S.	151.6	93.2	2.1
J. R.	151	103.4	2.45
M. P.	141.5	93.2	4.9

It will be noted that in those instances in which electrolyte change occurred any one of a number of variations is possible, but in most instances the striking changes were the reduction in the blood levels of potassium and and chloride with an alkalosis, and with or without elevation of the blood sodium. The alkalosis and low blood chlorides were in no instance due to vomiting but rather were in some way associated with the disturbance of potassium metabolism, as suggested by McQuarrie[4] and rather confirmed by Willson and his group. The latter authors found on the basis of careful metabolic studies that the reduction in plasma potassium mirrored a marked depletion of the intracellular potassium stores. That this depletion in body potassium probably conditioned the chloride level is evidenced by the fact that following the addition of potassium citrate to the diet there occurred an increase in the plasma concentration of both potassium and chlorides. On the other hand, the administration of ammonium chloride alone failed to affect the blood chloride level.

The question then arises, are these blood electrolyte changes consistent with and explainable by hyperfunction of the adrenal cortex? If there is an increase in the formation of the salt retaining hormone in these patients one may reasonably expect the electrolyte changes outlined above. Actually, the fact that such electrolyte changes occur would in itself indicate such an increase. More concrete evidence, however, of the existence of such cortin like substance in the blood and urine of patients with Cushing's syndrome was provided by the studies of Anderson and Haymaker.[8,9] These authors demonstrated that extracts of the blood and urine of patients prepared by a method used for extracting adrenal cortical hormone from adrenal tissue prolonged the lives of adrenalectomized rats beyond the survival periods of untreated controls. Actually, the salt retaining effect of 1 cc. of blood was found to be equivalent to 4 to 6 grams of fresh adrenal tissue, and in one instance a twenty four hour urine specimen contained the equivalent of approximately 400 grams of adrenal gland.

Further evidence, although more indirect in character, concerning the thesis just outlined is provided by the work of Thorn and his group[10,11,1] on the effect of desoxycorticosterone acetate on the urinary excretion of potassium. These investigators found that the administration of this compound resulted in a lowering of the serum level of potassium and an increase in the urinary excretion of this ion. This phenomenon was observed to occur in normal as well as in adrenalectomized animals and has been noted by many authors in the treatment of patients with Addison's disease.

Still more evidence is afforded by the experimental use of adrenocorticotropin and cortisone in the human subject. In these studies a hypochloremic alkalosis associated with a high serum sodium and a low serum potassium is not infrequently observed. The genesis of this pattern is probably related to the excessive urinary loss of chlorides and to a lesser extent potassium with a consequent depletion of the intracellular base. This is quite consistent with the experimental work of Darrow who has demonstrated the occurrence of a hypochloremic alkalosis in the experimental animal on a low potassium diet.[37]

One may therefore conclude that the reduction in serum potassium and the elevation of serum sodium when present in Cushing's syndrome is the result of increased formation of adrenal steroids exercising salt retaining effects. The lowering in the blood chloride levels is probably a function of the depletion of potassium stores and the alkalosis is of an acid deficit type secondary to the reduction in chlorides.

This of course explains only those few instances of Cushing's syndrome in which alterations in blood electrolytes occur. Does the same mechanism operate in those patients who manifest no changes in the blood electrolyte pattern? It must be evident that some limiting factor, some compensatory mechanism, must be operative in both groups. If such were not the case the unrestrained formation of excessive quantities of cortin like substance would result not only in much more marked sodium retention and potassium diuresis but in overt physical phenomena incidental to these changes. With a decrease in the urinary excretion of sodium there should occur a corresponding fluid retention with the development of progressive and uncontrollable edema. Patients with adrenal cortical tumors frequently

manifest some edema, but never to the extent where it constitutes a disturbing clinical problem We achieve a partial insight into the nature of this compensatory mechanism as a result of some observations noted in our laboratory [13] We observed that in normal individuals the intravenous injection of salt following the intramuscular injection of a single dose of desoxycorticosterone acetate resulted in a considerable retention of injected salt above that seen prior to the injection of the hormone In contrast to these results the patients with Cushing's syndrome showed a pronounced sodium chloride diuresis It is interesting to note that Kuhlmann and his coworkers[14] and Ragan and his group[15] reported the production of a diabetes insipidus like picture following the daily intramuscular administration of 20 to 25 mgm of desoxycorticosterone acetate to normal dogs These observations were confirmed by Mulinos and his coworkers [16] even though this latter group employed considerably smaller dosages of the hormone

The evidence then would suggest that the excessive salt retaining hormone formed is rapidly converted into another substance lacking salt retaining effects There is also the possibility that the formation of excessive amounts of salt retaining hormone stimulates the production of diuretic hormones either in the adrenal itself or in some other gland notably the anterior lobe of the hypophysis The first of these possibilities that is the conversion of the desoxycorticosterone into a non salt retaining hormone would at least seem theoretically feasible in view of the close chemical similarity between desoxycorticosterone and other adrenal steroid hormones which have relatively little salt retaining effect It is no accident on the part of nature that the adrenal cortex actually manufactures a number of hormonal fractions many of which have antithetical pharmacologic effects These fractions, some of which have been isolated in crystalline form serve as a finely balancing mechanism which controls the production of exaggerated phenomena in one direction or the other

It might be anticipated that this compensatory mechanism is not entirely effective in those individuals who manifest a disturbance in the blood electrolyte pattern This is borne out by our observations in 2 cases of adrenal cortical tumors in which there was a considerable elevation of the plasma sodium In both instances the injection of desoxycorticosterone under the conditions of our experiment failed to produce a sodium chloride diuresis [83]

The blood calcium and inorganic phosphorus levels were essentially normal in most instances of Cushing's syndrome reported in the literature in which these determinations were made In the group of cases studied in our clinic no deviations from the normal in respect to these blood constituents were observed In McQuarrie's case [4] there was a questionable slight reduction both in the blood level of calcium and phosphorus The details of the relationship of the osteoporosis to calcium and phosphorus metabolism have been discussed elsewhere in this book

Hormonal Studies in Adrenal Cortical Hyperfunction —It is well established today that normal men and women excrete both androgenic and estrogenic compounds in the urine These compounds however have their origin not only in the gonads but also in the adrenals These latter glands elaborate therefore both androgens and estrogens The urine of castrated males and ovariectomized females have slight but definite andro

genic and estrogenic activity[17] In addition to physiologically active compounds which are excreted in the urine and which have their origin in the adrenals inert compounds probably degradation products of more active substances elaborated in the adrenal are also found in the urine Some of these compounds are found in the urine of normal men and women Other substances are present only in pathologic states associated with hyperactivity of the adrenal cortex It is of interest too, that the actual androgenic content of hyperplastic or neoplastic adrenal glands is extremely low despite the fact that they may give rise to excessive amounts of androgenic substances in the urine[18 19] It would seem then that only minute amounts of such substances are stored in the gland where they are manufactured

To date, 28 steroids have been isolated from the adrenal,[85 86] of these 11 have proved to be biologically active Except for the androgenic compounds and estrone the physiologically active steroids are Δ_4 pregnanes the inactive compounds are allo-pregnanes The physiologically active steroids isolated include compounds A B E, and F, desoxycorticosterone and progesterone all these compounds affecting either carbohydrate or salt and water metabolism as well as androstane 3β 11β diol 17 one Δ_4 androstene-3 11-17 trione (adrenosterone), Δ_4 androstene-3 17-dione which are C 19 androgenic steroids and estrone, a C 18 compound Of these compounds adrenosterone has an androgenic activity equivalent to about 1/5 of that of androsterone as determined by the capon comb growth method and '11 hydroxyisoandrosterone about 1/30 that of androsterone 17 hydroxyprogesterone is about as androgenic as androsterone On oxidation it yields Δ_4 androstenedione which has even greater androgenic properties and which is chemically closely related to testosterone

Recent studies have revealed the large variety of steroids that may appear in the urine in normal and in various abnormal states Dobriner and his associates have recently reported on 3α ketosteroids and 7β ketosteroids isolated from the urine[89 90] of normal and diseased patients

Among the neutral 17 ketosteroids isolated from normal urine are androsterone etiocholan 3α-ol 17 one androstane 3α 11 diol 17 one etiocholan 3α-ol 11 17-dione and $\Delta_{9\,11}$ etiocholan 3(α)-ol 17 one all alcoholic ketosteroids The 3β 17 ketosteroids isolated include dehydroisoandrosterone and isoandrosterone The ketonic nonalcoholic steroids include $\Delta_{3\,5}$ androstadien 17 one Δ_2 androstene 17 one and 3 chloro Δ_5 androsten 17-one In the nonketonic alcoholic fractions there has been found Δ_5 androsten 3(β) 17(α) diol and etiochlorane 3(α) 17 diol In addition pregnane 3α 20α-diol and estrogens have been found

Androgenic and Estrogenic Urine Assays —How can this data be utilized for clinical purpose ? In suspected instances of hyperfunction of the adrenal cortex it is obviously impossible in routine chemical studies to attempt to isolate and to determine the amounts of the various individual fractions Attempts are therefore made to determine the total androgenic and estrogenic activity of the urine specimen without identifying the individual constituents For these purposes androgenic activity is measured by the capon comb growth technic[40] and estrogenic activity

23

on spayed adult female rats according to the vaginal spread technic of D'Amour and Gustavson.[31] The androgenic measure technic consists briefly of injecting 7 capons daily for five days with 1 cc. each of the unknown (extracted from the urine) in oil. The length and the height of the combs are measured on the first and the sixth days and the average total growth obtained. A standard containing 100 gammas of androsterone or its equivalent is assayed in parallel with the unknowns, using the same number of capons. Then, according to the curve obtained by Gallagher and Koch,[30] the total capon units are determined. The estrogenic assay is conducted by injecting the unknown preparation (extracted from the urine) into 10 adult spayed albino rats. Ten additional rats are injected with 0.88 to 2.0 gammas of a standard theelin preparation, as controls. Vaginal smears are made forty-two, forty-six, and fifty-two hours after the time of injection and examined under low power. The test is considered positive when the smear is free from leukocytes and contains aggregates of mononucleated epithelial cells. From the percentage of animals showing a positive reaction, the concentration of estrogenic units is read from the standard curve of D'Amour and Gustavson[31] in terms of gamma of theelin as compared with the standard run in parallel. More recently chemical estimation of the estrogens based on a fluorometric method has been employed.[91]

The normal values for androgen and estrogen excretion in the urine vary considerably. The values obtained by Gallagher and his coworkers[32] are probably most nearly correct. They found that the average daily urinary excretion of androgen in males was 63 to 68 international androgen units and in females 42 to 56 units. Women therefore excrete two-third as much androgenic material as men. Dingemanse, Borchard and Laqueur[33] found that up to the age of forty both men and women excrete about the same amount of androgen, *i.e.*, 40 to 50 international units per liter. Each international unit is equal in androgenic activity to 1/10 milligram of androsterone.

The average daily urinary excretion of estrogens, determined as gammas of theelin, is 9 to 12 gammas for men and 18 to 36 gammas for women. The daily urinary excretion of estrogenic material is influenced by the time relationship to the menses in women. Thus, peaks of estrogenic hormone excretion are reached twelve to fifteen days after the onset of menstruation and again four to eight days before the next period, according to Frank.[34] Gallagher and his coworkers[3] vary this somewhat to include the period seven to fifteen days after the onset of menses and six to twelve days before the next bleeding.

In general, there is a very marked daily variation in the urinary excretion of both androgens and estrogens, and the clinical significance of 1 or 2 twenty-four hour urine assays must not be unduly emphasized. In hyperfunction of the adrenal cortex there is a surprising lack of correlation between the clinical picture and the sex hormone assays in the urine. Thus, Kenyon and his group[35] found that in 16 patients with virilism normal amounts of androgenic and estrogenic substances were excreted in all but 1 instance. This exception was a patient with a carcinoma of the adrenal cortex who excreted unusually large amounts of androgenic material.

amounting to 400 international units per day Dorfman and his coworkers[36] reported 10 instances of virilism in which urinary androgenic assays were made In 1 of this group a patient with adrenal hyperplasia there was a marked increase in the urinary androgens The remaining 9 patients excreted normal quantities of androgenic substances Simpson del Kremer and Macbeth [37] in 12 instances of virilism found a marked excess of urinary androgens in 5 patients and a moderate excess in 4

In instances of carcinoma of the adrenal cortex there may occur either a marked increase in the urinary excretion of androgens or of estrogens regardless of the sex of the patient Thus Crooke and Callow [19] in 2 instances of adrenal carcinoma with the characteristic of Cushing s syndrome found inordinately excessive quantities of urinary androgens Burrows and his coworkers [1] found a moderate excess of androgenic hormone in the urine of a male with marked evidence of feminization due to a carcinoma of the adrenal cortex Slot[13] described the instance of a woman with virilism due to an adrenal carcinoma in which 2200 international units of comb growth stimulating material were obtained from a liter of urine In addition there was a slight increase in the urinary excretion of estrogens

Frank[35 39] called attention to the fact that in instances of adrenal carcinoma excessive quantities of estrogenic hormone may be excreted in the urine Thus in 4 instances of adrenal carcinoma he found inordinately large amounts of such substances in the urine (1000 to 10 000 mouse units per day) while in 15 instances of Cushing s syndrome due to adenomata or hyperplasia of the adrenals no such excess of urinary estrogenic activity was noted Simpson and Joll[40] report the case of a male with an adrenal cortical carcinoma with marked signs of feminization in whom the daily urinary excretion of estrogenic hormone exceeded 6000 mouse units per liter However large quantities of urinary estrogens have been noted in instances in which the adrenals were not the seat of a carcinomatous growth Thus Saphir and Parker[41] report the case of a fifteen year old girl with hypertrichosis obesity and amenorrhea who excreted 5000 mouse units of estrogenic substance per liter of urine At operation the adrenals were found to be normal Similarly not all cases of adrenal carcinoma exhibit this marked outpouring of urinary estrogens [1]

It will be evident even from this casual survey that the relationship of the urinary androgens and estrogens to the clinical picture is at present a confused and disorganized one In part it is perhaps due to the paucity of clinical material studied so that correlations cannot as yet be made on a statistically significant basis In part, too there are unquestionably many additional androgenic and estrogneic urine fractions and their degradation products which may be inert and which have not been isolated and identified One would expect that there would be a direct and immediate correlation between the degree of masculinization and the amount of urinary androgens and between the intensity of feminization and the excretion of urinary estrogens This is an attractive hypothesis but except for occasional instances it is infrequently observed as a clinical occurrence It is true that in some instances of carcinoma of the adrenal cortex with virilism there is an excessive amount of comb growth promoting substance while in at least 1 instance of feminization in a male due to a malignant adrenal corti-

cal neoplasm large amounts of estrogenic hormone were noted in the urine But even larger quantities of urinary estrogens have been observed in women with marked masculinization,[29] while most instances of virilism fail to show any marked increase in urinary androgens While the significance of the urinary excretion of the sex hormones must not be minimized it is obvious that other factors at present obscure, must play an important role in determining the character of the clinical picture Kenyon[35] has suggested that the ratio of male to female urinary constituents may be more significant than the gross amounts Perhaps even more important although less demonstrable of proof is the amount of androgenic or estrogenic material actually used The quantities excreted in the urine must of necessity represent an overflow of the actual hormone or its degradation products and under such circumstances are no index of the amount of hormone physiologically utilized

In any event for purposes of clinical diagnosis the following must be borne in mind Most patients with the adrenogenital or Cushing's syndrome in the absence of an adrenal cortical tumor will show no or a slight increase in the urinary androgens or estrogens Some patients will show a moderate increase of either one or the other Patients with malignant adrenal cortical tumors usually show excessive quantities of either urinary androgens or estrogens At present no clinical correlation can be established between the degree of masculinization or feminization and the amount of androgenic or estrogenic factors observed in the urine

TABLE 19 —ANDROGEN AND ESTROGEN URINARY EXCRETION IN HYPERFUNCTION OF THE ADRENAL CORTEX

Diagnosis	*Daily Excretion of Urinary Androgens*	*Daily Excretion of Urinary Estrogens*
Carcinoma of Adrenal Cortex	May be excessive	May be excessive
Benign Tumor of Adrenal Cortex	Usually normal May be slightly to moderately increased in Cushing's syndrome May be markedly increased in virilism	Usually normal May be slightly to moderately increased
Hyperplasia of Adrenal Cortex	Usually normal May be slightly to moderately increased	Usually normal May be slightly to moderately increased
Pituitary Basophilism	Usually normal May be slightly to moderately increased	Usually normal May be slightly to moderately increased

It should be emphasized again that the biologic determination of urinary androgens and estrogens is specific for neither one substance nor the steroids originating from a single gland What we are determining in effect are those steroids originating from the gonads and the adrenals which exercise definite androgenic or estrogenic activity The biologic assay then has the disadvantage of not including those steroid compounds present in the urine and under certain circumstances in abnormal quantities which

manifest neither androgenic nor estrogenic activity Such a compound for example is 3 α hydroxyetiocholane 17-one This compound may be considerably increased in the urine and still remain undetectable by the usual biologic assay methods This latter method has the further disadvantage in being time-consuming and rather complicated to perform

Urinary 17 Ketosteroids —The development of a color reaction for androgens by Zimmermann[4 43] created the possibility of a chemical test for steroids which might parallel the biologic assay method This color reaction was further modified by Wu and Chou[44] and by Callow Callow and Emmens[45] for application to urinary extracts The latter authors showed that the chemical test roughly paralleled the biologic assay method The reaction is based on the fact that substances containing an active ketone and methylene group—CH CO—in the presence of alkali and meta-dinitrobenzene produce a red color which may be used for quantitative assay In the presence of ketosteroids the color produced depends upon the position of the ketone group Steroids with a ketone group on the 17th carbon atom the so-called 17 ketosteroids develop an intense absorption band with a maximum in the green while this was not true of those steroid compounds in which the ketone group was attached to the 3rd 6th or 20th carbon atom[45]

The test then as used for our purposes is for the determination of the non phenolic neutral 17 ketosteroids The determination of the estrogenic factor is not included in the test despite the fact that estrone is a 17 ketosteroid Being a weak phenol however it is removed by washing with alkali which is a step in the extraction process The determination of the 17 neutral ketosteroids is actually not a test for androgens although it may parallel the latter Thus 3 α hydroxyetiocholane 17-one is a 17 neutral ketosteroid although not an androgen while testosterone, which is an androgen is not a 17 ketosteroid The most common 17 ketosteroids thus far isolated from normal and pathologic urines and which are included in the chemical tests are chiefly 1 Androsterone 2 Dehydroisoandrosterone 3 3-α hydroxyetiocholane 17-one 4 $\Delta_{3,5}$ androstadiene-17 one 5 Isoandrosterone and 6 3 α hydroxyandrosten 17-one

Bearing in mind the limitations of the test particularly the fact that estrogenic factors and perhaps other fractions which are not 17 ketosteroids are not included in the color reaction the method has a considerable field of usefulness It is considerably easier to perform than is the biologic assay and may yield information of value in adrenal and pituitary dysfunction

In another chapter in this book we have outlined the normal values for the urinary ketosteroids in males and in females of varying age groups Briefly the normal values are somewhat higher in men than in women since these compounds are elaborated both by the adrenals and the *male gonads* Actually the difference between the males and the females represents approximately 5 mgm of 17 ketosteroids for twenty four hour urine volume This difference ostensibly reflects the quantity of 17 ketosteroids normally manufactured in the male gonads The amount excreted in the urine becomes progressively larger from childhood up to the age of forty

and then begins to decrease. The average urinary output of children from four to seven years of age is 1.3 mgm. per twenty-four hours; from the age of seven to twelve 4.0 mgm.; from twelve to fifteen 8.2 mgm.; adult women, 10.2; and men 15.0 mgm. These figures represent the *average* urinary excretion. In Fraser's series,[46] the range in women varied from 5.1 to 14.2 mgm. per twenty-four hours, while in men it varied from 8.1 to 22.6. These correspond fairly closely to the results obtained by Chou and Wang,[47] whose range of normal values extended from 5.9 to 18.8 mgm. twenty-four hours. Callow and his coworkers[48] found that the range varied from 6.0 to 15.0 for males and 6.9 to 12.6 mgm. for females. The day to day variations in normal individuals is relatively slight. Fraser and his group[46] found a daily variation in the same individual of approximately 1 to 3 mgm. Fluctuations have generally not been found to correlate to any degree with the menstrual cycle.[33] Some investigators, however, have reported the occurrence of higher titers premenstrually,[33,49,50] while others have reported an increase postmenstrually.[37,51] Hamblen and his group[52] have found that the average values for 17-ketosteroids excretion are lower during the bleeding phase than during the interval phase of the cycle.

The urinary excretion of 17-ketosteroids may be expressed in terms of milligram equivalents of crystalline androsterone, as suggested by Fried and Whidden,[53] as the "milligram sterone" unit of Callow and his coworkers,[48] which is essentially the same, or in terms of international androgenic units. 1 milligram of crystalline androsterone is equivalent to 10 international units.

The urinary excretion of the 17-ketosteroids in various pathologic states have been reported extensively in the literature. Excellent reviews are provided by the reports of Fraser and his coworkers,[46] Hamblen and his group[5] and Engstrom.[8] Low urinary 17-ketosteroids have been noted in malnutrition, whether due to anorexia nervosa or impaired intestinal absorption such as occurs in chronic terminal ileitis, in infections, surgical operations and in fact in almost any sort of nonspecific trauma.[46] Similarly, low excretion values have been noted in liver disease and in anemia. It is interesting that in these various groups, although there is a quantative reduction of these compounds in the urine, some are *always* present. This s in contrast to the results obtained in both Addison's disease and in pituitary cachexia (Simmonds' disease). In these instances the urinary 17-etosteroids frequently disappear entirely.

In instances of hyperfunction of the adrenal cortex, the quantity of 17-etosteroids excreted in the urine is dependent upon the nature of adrenal athology. The highest urinary excretion values are obtained in instances f adrenal cortical carcinoma. In this group the amount of 17-ketosteroids xcreted in the urine is usually excessive, that is over 60 mgm. per twenty-our hours, although normal figures are sometimes observed. In patients ith virilism who have no overt adrenal pathology, the urinary ketosterds are frequently normal in postpuberal patients. In prepuberal virilism n the other hand, the urinary excretion of 17-ketsoteroids is moderately creased. In approximately 35 per cent of this entire group of virilized tients there may be a slight increase, that is up to 25 to 30 mgm. per

twenty four hours Occasionally such patients will excrete a moderate excess in the urine over 30 mgm in twenty four hour urine volumes Most patients with Cushing s syndrome in whom the adrenals show no overt changes will excrete normal amounts of the 17 neutral ketosteroids Only rarely may an occasional patient show a slight or moderate increase Patients with adrenal cortical hyperplasia usually have considerable amounts of ketosteroids in the urine and occasionally even in excessive quantities Rarely however does this group approximate the quantitative excretion observed in patients with malignant adrenal cortical tumors[5] This is by no means a hard and fast rule since considerable overlapping may occur in all groups Very high urinary ketosteroid titers nevertheless strongly bespeak the presence of malignant adrenal tumor

In the virilizing syndrome associated with adrenal cortical tumor the excretion of urinary 17 ketosteroids may be markedly increased In Cushing s syndrome associated with an adrenal cortical adenoma the urinary 17 ketosteroids may be normal or increased Unfortunately in the latter group too few such cases have been reported for any generalization to be made

The results of the 17 ketosteroid excretion in the urine in instances of feminization are exceedingly meager This is of course due to the rarity of this syndrome Burrows and his coworkers[4] have reported a very high urinary 17 ketosteroid excretion in the case of a male with marked feminization due to a malignant adrenal cortical tumor

TABLE 20 — URINARY EXCRETION OF 17 KETOSTEROIDS IN HYPERFUNCTION OF ADRENAL CORTEX

	Number of Cases	*Normal Amount*	*Slight Increase*	*Moderate Increase*	*Excessive Increase*
Virilism (No overt Adrenal Pathology)	64	35	24	5	0
Cushing s Syndrome (No overt Adrenal Pathology)	14	10	2	2	0
Virilism with Cushing s Syndrome (Adrenal Cortical Hyperplasia)	12	2	1	5	4
Virilism with Cushing s Syndrome (Adrenal Cortical Carcinoma)	14	1	0	3	10

With the successful removal of the tumor or the amelioration of the signs and symptoms of adrenal cortical hyperfunction through any therapeutic measure there occurs a prompt decrease in the urinary excretion of of these steroid compounds The occurrence of metastasis is frequently first manifested by a reappearance of excessive quantities of urinary ketosteroids

For purposes of clinical diagnosis the determination of total urinary 17 ketosteroids is entirely adequate Talbot Butler and MacLachlan[54] have

suggested, however, that in adrenal cortical carcinoma there occurs particularly an increase in the urinary excretion of the beta ketosteroids. It will be remembered that the total ketosteroids consist of alpha and beta fractions. The terms alpha and beta refer essentially to the spatial position of the 3 hydroxyl group and the chemical separation of these two components is dependent on the fact that the beta ketosteroids may be precipitated with digitonin leaving the alpha ketosteroids in solution. The beta ketosteroids, which in normal urine refer primarily to isoandrosterone and dehydroandrosterone, arise apparently entirely from the adrenal cortex. The *alpha ketosteroids are elaborated both by the adrenal cortex and by the male gonads.* In normal individuals approximately 10 to 15 per cent of the total neutral 17 ketosteroids consists of the beta fraction.[45,51,55,56,57,58] In adrenal cortical carcinoma this percentage is frequently considerably increased.

The Urinary Corticoids. — The urinary excretion of the corticoids may be markedly increased following trauma or stress and the increase represents an adrenal response to injury.

These substances may be considerably increased in Cushing's syndrome whether there is no overt adrenal pathology or whether adrenal hyperplasia or tumor is the underlying cause. In virilizing syndromes associated with adrenal cortical disease the excretion of these steroids is normal, although one instance of a high urinary excretion has been reported in an adult.[illegible] The exception to this latter general rule is in infants with congenital adrenal cortical hyperplasia. In this group high excretions are often noted.

The Diagnosis of Adrenal Cortical Hyperfunction. — We are faced with essentially the following problems in the diagnosis of adrenal cortical hyperfunction:

a) In a patient presenting a particular clinical picture, are we dealing with an instance of overactivity of the adrenal cortex?

b) In a patient presenting clinical evidence of such overactivity, is it due to adrenal cortical hyperplasia or tumor, or is it secondary to primary pituitary disease such as occurs in pituitary basophilism?

In regard to the first problem, it must be remembered that there are a variety of pathologic conditions which may simulate clinically the picture produced by increased adrenal cortical activity. Such cases occur with arrhenoblastomas and other tumors of the ovary, hyperostosis frontalis interna, pineal tumors, thymic tumor, and pituitary tumors. In the identification of the cases due to adrenal cortical disease we must resort to careful clinical, laboratory and roentgenologic studies. The clinical investigation must consist of a well-documented history and a thorough physical examination. The age of onset of the symptoms, the duration of the disease, the presence or absence of signs of virilism or feminization or genital abnormalities, the premature development of the secondary sex characteristics, the presence or absence of those external phenomena including hypertension characteristic of Cushing's syndrome, the presence or absence of abdominal and pelvic mass, help roughly to categorize the patient and provide the initial direction for further study. The significant laboratory studies include the determination of the urinary 17 ketsoteroid and more recently the assay of the urinary corticoids chemically and bio

logically salt tolerance studies blood electrolyte determinations glucose tolerance curves and the presence or absence of polycythemia The x ray studies should include investigation of the sella turcica for enlargement or destruction indicative of pituitary tumor studies of the long bones for osteoporosis intravenous pyelography and perirenal insufflation for visualization of a possible adrenal tumor or adrenal cortical hyperplasia

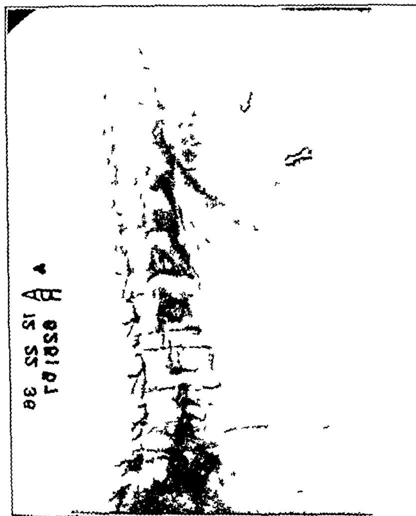


Fig 26 — Adrenal cortical tumor outlined by perirenal insufflation in a patient with Cushing's syndrome

When the diagnosis of adrenal cortical hyperfunction is established the determination of the presence or absence of an adrenal tumor is dependent upon the following measures

a) The palpation of an abdominal mass
b) Perirenal insufflation studies demonstrating the existence of an adrenal mass
c) The pyelographic demonstration of a suprarenal mass
d) Excessive urinary quantities of 17-neutral ketosteroids, estrogens and urinary corticoids
e) Finally, in those instances in which the other studies are equivocal it is often necessary to resort to an exploratory operative procedure to determine the possible presence of an adrenal tumor



Fig. 27.—Case of Cushing's syndrome. Small tumor of adrenal (adenoma). Oblique view. (Mencher, courtesy of Jour. Am. Med. Assn.)

Differential Diagnosis.—*Pituitary Basophilism.*—True pituitary basophilism must be interpreted as a disease in which most of the clinical manifestations are due to secondary hyperactivity of the adrenal cortex. Often there is an absence of any gross or microscopic changes in the adrenals. Just as often hyperplasia is noted. The clinical and laboratory picture produced is frequently identical with that observed in tumors of the adrenal cortex. It differs from the latter only in that virilizing mani-

festations are minimal and the urinary 17 ketosteroids are usually normal or slightly elevated and that no adrenal masses can be demonstrated either by the technic of perirenal insufflation or intravenous pyelography. Frequently operative procedures must be resorted to in order to exclude the existence of an adrenal tumor. Generally speaking, when an adult female presents evidences of mild virilism and the metabolic disturbances of Cushing's syndrome but shows no increases in the urinary excretion of 17 neutral ketosteroids and 11-oxygenated steroids and no evidence of ad



Fig. 28.—Tumor of the right adrenal cortex demonstrated by perirenal insufflation. Note normal adrenal on the opposite side.

renal masses by perirenal insufflation, the probabilities are that this patient has no adrenal cortical tumor. Adult males who manifest the evidences of a Cushing's syndrome but show no signs of extensive feminization rarely have adrenal tumors as the etiologic factor. In the presence of marked feminization, however, an adrenal cortical tumor has almost always been found. The existence of Cushing's syndrome in children is similarly usually associated with the presence of an adrenal tumor.

Arrhenoblastomas of the Ovary.—Arrhenoblastomas of the ovary are old tumors of the ovary which produce virilism. Women afflicted with this disease usually develop amenorrhea, extensive hirsutism, hypertrophy of the clitoris, and in general become masculinized. Their libido may be normal but is frequently reduced. No case has been reported in a patient under the age of fifteen. To this point it is evident that arrhenoblastomas are indistinguishable clinically from the adrenogenital syndrome. However, patients with the former tumors practically never develop the metabolic disturbances characteristic of Cushing's syndrome. Thus hypertension, osteoporosis, impaired glucose tolerance, characteristic obesity, acne, and ecchymoses are not seen in patients with arrhenoblastomas. Striae may occasionally be observed. The urinary excretion of the neutral 17-ketosteroids is within normal range. There are a group of patients, 19 in number, in which presumably adrenal rests of the ovary have been noted. In these patients some of the evidences of Cushing's syndrome have been observed in addition to virilizing manifestations.[93]

The distinction, then, between patients with Cushing's syndrome with or without an adrenal cortical tumor and patients with an arrhenoblastoma of the ovary is relatively simple. The difficulty lies in the distinction between this latter condition and cases of adrenogenital syndrome in which the *metabolic disturbances* are lacking. The presence of a pelvic adnexal mass points usually to an ovarian tumor, although Saphir and Parker[4] reported the instance of a fifteen year old girl with hypertrichosis, obesity and amenorrhea, whose extirpated ovary showed the presence of rests of adrenal-like cells. This patient, however, excreted large quantities of estrogenic and androgenic substances in the urine. Not infrequently, however, the arrhenoblastomas may be small tumors and not readily palpable. Occasionally, too, tumors originating from pelvic adrenal rests could by their location suggest arrhenoblastomas. However, these are rare instances and in general the coincidental presence of virilism and an adnexal mass points to an ovarian tumor, usually an arrhenoblastoma. Of course, the problem is equally simplified by the demonstration of an adrenal mass by perirenal insufflation. Nevertheless, the question often can be settled conclusively only by an exploratory laparotomy. Every patient with a true adrenogenital syndrome should be subjected to an exploratory procedure and where an adrenal tumor has not been previously determined to be present the possibility of an ovarian tumor should be borne in mind.

Hyperostosis Frontalis Interna (Morgagni Syndrome, Stewart-Morel Syndrome, Metabolic Craniopathy.)—This disease, so ably reviewed by Knies and LeFever,[59] usually occurs in women, generally in the fifth decade, and is characterized by rather typical bony changes. These changes usually involve the frontal, parietal, or occipital portions of the skull and are due to

a noninflammatory deposit of new bone on the internal table of the *squama frontalis* occasionally extending to the orbital plate the falx and the *squama parietalis* The hyperostoses are usually symmetrical and there is an associated increase in the bony thickness of the internal table and diploe while the external plate is spared There may be considerable variation from this classical picture such as the presence of increased density and thickness of the diploe of the *squama frontalis* only or a diffuse thickening of the diploe of the entire calvarium without involvement of either table In addition to these rather characteristic roentgenologic bony changes these patients may manifest obesity virilism and hirsutism They also frequently show polyphagia polydypsia polyuria a decrease in glucose tolerance and disturbances in menses Most of the patients have severe headache and a considerable number show neurologic changes such as convulsions, loss of sense of smell involvement of the 5th and 7th cranial nerves and occasionally hemiparesis and even hemiplegia A small percentage have hypertension

From this brief description it is evident that it may be confused with the syndrome produced by adrenal cortical hyperfunction However the differentiation is based on the later age of onset of Hyperostosis Frontalis Interna the characteristic *x* ray picture of the skull the absence of diffuse osteoporosis the lack of typical response to the salt tolerance test completely normal blood electrolyte pattern negative perirenal insufflation and normal urinary 17 ketosteroid excretion The most important objective laboratory observations in the differential diagnosis between the two groups is the typical *x* ray picture of the skull and the normal salt tolerance response

Thymic and Pineal Tumors —Certain malignant tumors of the thymus are associated with evidences of virilism and the metabolic disturbances of Cushing s syndrome Three such cases were originally reported by Leyton Turnbull and Britton[53] and in each instance marked adrenal cortical hyperplasia was found in addition to a carcinoma of the thymus The syndrome produced in these patients is indistinguishable from true Cushing s syndrome and in fact the clinical manifestations are probably due to the associated adrenal hyperplasia The pre mortem identification of this group is dependent on the recognition of the existence of a thymic tumor Two more such cases have since been reported[54]

Pineal tumors usually teratomas offer relatively little diagnostic difficulty These are almost always instances of pubertas precox in young boys They generally lack the typical obesity striae and hypertension and usually manifest signs of an intracranial lesion The precocity is not due to the pineal tumor *per se* but results from the destruction of midbrain and hypothalamic centers by the invasive tumor

It should be stressed again that patients may present all the objective evidences of an adrenogenital syndrome with or without Cushing s syndrome and demonstrate no pathologic abnormalities Finally there is an additional group of patients relatively large in size in whom hirsutism some obesity and frequently some hypertension are present who do not fall into any of the categories described above These patients constitute a cosmetic problem essentially They are characterized by their general

well being the failure of the symptoms to progress and the absence of any concrete physical or laboratory findings to account for their state Close investigation of their family history will almost invariably reveal similar ancestral physical abnormalities

Treatment and Prognosis — The therapeutic measures which have been employed fall essentially into 3 groups

a) The use of various hormonologic agents notably estrogenic hormone and testosterone
b) Irradiation therapy to the pituitary and adrenals
c) The surgical approach

Hormone Treatment of Adrenal Cortical Hyperfunction —Gill[61] and Dunn[62] have employed large doses of estrin in the treatment of patients with Cushing's syndrome Their patients have shown some relief of the subjective symptoms but no change in either the physical phenomena or the course of the disease In our clinic we have used estrogenic hormone in several instances of well-defined Cushing's syndrome with entirely negative results Albright and his group[63] reported observations, following the use of estrin therapy similar to ours

Albright and his coworkers[63] have advocated the use of testosterone in the treatment of patients with Cushing's syndrome The rationale of the therapy according to these authors is based on the fact that many of the features of Cushing's syndrome are the result of protein shortage The protein shortage being due to the formation of excessive quantities of that adrenal cortical hormone fraction which promotes gluconeogenesis through the conversion of protein into sugar As a result of such vigorous conversion there is not only too much sugar but too little protein The object of therapy then was to establish a positive nitrogen balance The substance par excellence to promote a positive nitrogen balance is testosterone Three patients with Cushing's syndrome two of whom were proven to have grossly normal adrenals at operation were treated with 25 to 50 mgm of testosterone daily for several months In each instance there followed a consistent alteration of the metabolic pattern There occurred a marked decrease in the nitrogen and phosphate excretion in the urine a gradual decrease in urinary calcium with an increase in calcium balance and eventually a significant rise in the serum phosphatase With these metabolic changes the patients improved considerably There was a gain in weight and strength the skin became thicker bruised less readily and there was a disappearance of the reddish hue In 1 of the 3 patients, treatment resulted in improvement in carbohydrate metabolism and return of the menses No effect was noted on the hirsutism or the hypertension There may have occurred some increase in the density of the bone[64] According to Snapper[9] improvement of the protein metabolism resulting from the use of testosterone in this disease causes a halt in the progression of the osteoporosis The pain frequently disappears no new fractures develop but despite the clinical improvement recalcification of the skeleton is hardly ever observed roentgenologically

Our own limited experience with testosterone has by no means been so satisfactory There possibly occurred some increase in the well being of the patients but no well-defined objective or even subjective changes could

be demonstrated However the results obtained by Albright and his group certainly warrant more extensive and critical investigation of the use of this compound in the treatment of this disease

X ray Treatment —It was inevitable that *x* ray therapeutic measures be introduced in a disease where definite pathologic changes were not always demonstrable and when present were not readily accessible surgically Cushing[65] in his original publication described the instance of a man with severe basophilism who responded dramatically to irradiation of the pituitary The patient received 4 *x* ray treatments on four successive days Since then repeated individual instances have been reported in the literature in which improvement to varying degrees has been obtained following pituitary irradiation The most striking was the case reported by Jamin[66] of a fourteen year old patient in whom apparently complete cure followed such treatment Of course the reports of isolated instances are apt to be misleading since individual therapeutic failures are generally not reported Freyberg and his colleagues[67] collected 18 cases of Cushing s syndrome from the literature treated with *x* ray to the pituitary Approximately one half of these patients were helped to varying degrees

In patients where an adrenal cortical tumor or hyperplasia is not present pituitary irradiation should be instituted Even when there is definite evidence of a growing pituitary neoplasm a course of *x* ray treatment should be given before surgical intervention is decided upon Some of the pituitary neoplasms are radiosensitive and in such instances regression of symptoms will occur following treatment However progressive retraction of the visual fields persistent and severe headache signs of increasing intracranial pressure continuing after *x* ray treatment are indications for surgical intervention It should be remembered that a period of four to six weeks may frequently elapse after *x* ray therapy before improvement becomes evident Basophilic tumors are usually small and practically never cause signs of increased intracranial pressure or roentgen evidence of encroachment on the Sella turcica

In the presence of adrenal cortical tumor *x* ray treatment of the pituitary *or of the adrenals* is ineffective

The Surgical Approach in Adrenal Cortical Hyperplasia —The results of surgery in patients with the adrenogenital syndrome or Cushing s syndrome due to bilateral adrenal cortical hyperplasia are fairly satisfactory The removal of one hyperplastic gland or considerable portions of both glands results in a recession of the signs and symptoms of the disease in a fair percentage of the cases The general exception to this is the instances of pseudohermaphroditism due to congenital adrenal cortical hyperplasia[68]

Koster and his coworkers[69] report the case of a twenty three year old girl who weighed 335 pounds She had marked hypertrichosis amenorrhea a deep rough masculine voice and marked frequency of urination Her blood pressure was normal At operation both adrenals were found to be enlarged and one was removed Two months later her menses were reestablished and the urinary frequency was considerably reduced Within one year after operation she had lost 145 pounds in weight and the hirsutism was rapidly disappearing

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ties of intravenous saline. In contrast to these results, those reported by Kepler and his group[74] are refreshingly different. Of 15 patients operated upon at the Mayo Clinic since 1924, all but 1 survived. The patient that died was operated upon in 1924, before modern methods of preparation were available. Nevertheless, the dangers and high mortality rate associated with this operation cannot be emphasized too strongly.

The postoperative deaths usually occur within six to forty-eight hours after the removal of the tumor and are due to shock. Now this shock is a curious kind of phenomenon, not responsive to the ordinary therapeutic measures which are available for treatment of the usual postoperative collapse. The shock which is observed in the adrenal cortical tumor patients is due to acute adrenal insufficiency. This insufficiency, however, is not associated with disturbances in electrolyte metabolism, but is probably due to the sudden deprivation of adrenal cortical factors as yet unidentified other than the salt retaining ones. We can be reasonably sure that the postoperative collapse is not related to any disturbance in electrolyte metabolism or blood sugar level, since no such disturbances are evident on chemical analyses of the blood. Significant in equal degree is the fact that the onset of shock occurs too soon postoperatively to be attributable to an Addisonian crisis in the ordinary sense. In the bilaterally adrenalectomized animals, to which these patients conceivably compare, and in the patient with Addison's disease, the loss of electrolytes and fluids occurs over a period of several days before crisis supervenes. The patient with an adrenal cortical tumor who is operated upon has an ample amount of circulating adrenal cortical hormone just prior to removal of the tumor. The excision of the growth is followed within a relatively few hours, and occasionally even within a few minutes, by this intractable vasomotor collapse. This period of time is entirely too short to permit of an adequate loss of electrolytes and fluid to produce the usual Addisonian crisis.

The shock which is observed in the tumor patients is not dissimilar to that frequently seen directly after bilateral adrenalectomy in the experimental animal. Kleinberg and his coworkers[75] have shown that this shock following adrenalectomy in the experimental animal can be prevented by a thorough infiltration with novocaine of the sympathetic elements adjacent to the adrenals prior to their extirpation. Section of the spinal cord at the first or second thoracic levels affords comparable protection against the vasomotor collapse. It might be desirable to follow the first of these procedures in patients with adrenal cortical tumors.

Not all patients with adrenal tumors develop acute postoperative adrenal insufficiency, but those who do invariably have a small atrophic contralateral adrenal. Such atrophic glands opposite the one containing the tumor are amply documented in the literature,[7, 76, 77, 78, 79, 80, 81, 82] and in at least two instances a total absence of the contralateral adrenal has been reported.[3, 83] It is of special interest and significance that generally only those patients with adrenal cortical tumors who clinically manifest evidence of Cushing's syndrome, particularly hypertension, have atrophic contralateral adrenals and develop postoperative shock. Those patients whose major clinical manifestation is virilism and who have none of the meta-

Broster[70,71] is a strong proponent of adrenal resection in cases of adrenal hyperplasia. He suggests removing as much of both hyperplastic adrenal glands as is consistent with safety and following this with irradiation of the pituitary. With this combined therapy he has obtained highly satisfactory results in the majority of instances of adrenal cortical hyperplasia. Walters and his group[72] on the other hand, have not been impressed with their own results following resection of a hyperplastic adrenal.

The removal of one hyperplastic adrenal is a relatively safe surgical procedure provided we bear in mind that the right adrenal is in direct contact with the inferior vena cava and hence, wherever possible, the left gland should be the one to be extirpated. In the removal of a hyperplastic gland we do not encounter the curious post-operative shock so frequently observed in the removal of an adrenal cortical tumor. The partial resection of both adrenals, however, is a much more complicated procedure and fraught with greater hazard. The removal of too much tissue may result in temporary or permanent adrenal insufficiency, while the removal of inadequate amounts of gland may not induce a satisfactory therapeutic response. There is the further danger that in attempting to resect portions of both glands intra-adrenal hemorrhage with adrenal destruction may occur. None of these pitfalls constitute really great hazards but nevertheless they are dangerous enough to warrant careful thought and the services of an experienced and skilled surgeon.

The Removal of Adrenal Cortical Tumors.—The successful removal of an adrenal cortical tumor usually results in a brilliant and complete cure of the disease. This is true in both the adrenogenital syndrome and Cushing's syndrome. In female patients the signs of masculinization will subside and refeminization will take place. The menses will be reestablished, the peculiar obesity will disappear, the florid and buffalo-like facies will return to normal and even a long standing hypertension may regress. The disturbance in carbohydrate metabolism reverts to normal and the skeletal structure becomes recalcified. In adult men the feminization will vanish. If the removed tumor is malignant and has already penetrated its capsule metastasis will eventually occur with a recurrence of all the original signs and symptoms.

These satisfying results unfortunately can be achieved only at great risk to the patient. In 1933 Cecil[65] pointed out that of the tumor cases collected from the literature that were operated upon 39 per cent died of shock soon after the operation. In 1937 Kulens and his coworkers[73] reported on 40 cases of adrenal cortical tumors of various types, 19 of whom died shortly after operation, this despite the fact newer methods of therapy with adrenal cortical extracts had been instituted in many instances. The percentage of fatalities is probably considerably higher since only isolated successful cases are reported in the literature.

In our own group of 9 patients that were operated upon 6 survived the removal of the tumor while 3 died shortly after the operation. Eight of the 9 patients including 2 of the 3 that failed to survive had been prepared preoperatively and treated postoperatively with large amounts of adrenal cortical extract intravenously and intramuscularly, and with large quanti-

administered subcutaneously, and 25 to 50 mgms of cortisone are given intramuscularly. If shock intervenes during the operation additional whole cortical extract and epinephrine are administered intravenously. After the initial immediate postoperative dose 10 cc of whole extract is administered intravenously and 10 cc subcutaneously and 25 mgm of Cortisone intramuscularly every two hours for 3 successive doses. The dosage of whole extract can then be reduced to 10 cc subcutaneously and 25 mgm of Cortisone intramuscularly every 6 hours for the remainder of the first twenty four hours after operation.

During the first twenty four hours then the patient has received approximately 190 cc of whole extract and 100 to 200 mgm of Cortisone. This quantity may be entirely too much or not enough depending on the individual circumstances. In general whole extract may be administered liberally enough without any fear of the development of undue complications. But desoxycorticosterone acetate must be given with great caution. The injudicious use of this compound particularly in the presence of intravenous fluid may result in heart failure, pulmonary edema or peripheral edema. It must therefore and at the first sign of waterlogging all therapy, including that of parenteral fluids must be temporarily discontinued.

If the patient has progressed satisfactorily during the first twenty four hours therapy for the second twenty four hours consists of 10 cc of whole extract and 25 to 50 mgm of Cortisone intramuscularly 3 times a day. If the patient survives the first forty-eight hours his outlook is good and thereafter both extract and supplementary salt are gradually reduced and eventually entirely discontinued. Extract and salt must be continued until we are entirely sure that the patient will not develop evidences of adrenal insufficiency. But by the same token therapy should not be unduly continued since such therapy will prevent compensatory hypertrophy of the remaining adrenal. A sudden drop in blood pressure, marked increase in pulse rate, rise in temperature are indications of the development of acute adrenal insufficiency and call for more vigorous therapy including transfusions and epinephrine. The development of hiccough, vomiting, restlessness or marked apathy after the operation are less urgent signs of impending insufficiency but nevertheless also indicate the need for more pressing treatment.

It is of interest that in the experimental animal adrenal hypertrophy may be induced by a variety of measures particularly by the use of the adrenotropic factor of the anterior pituitary and by diets high in protein.[84] Now that adrenotropic hormone is becoming more available a critical study of its value for this specific purpose will undoubtedly be undertaken.

More recently we have had occasion to prepare patients with adrenal cortical tumor for operation with ACTH and Cortisone. ACTH was used in an effort to stimulate the contralateral atrophic adrenal while the cortisone was intended to provide more immediate specific replacement therapy. One hundred milligrams of ACTH is given daily in 4 divided doses beginning 48 hours before the operation and is continued for several days during the post-operative period and gradually tapered off. Cortisone is given con

bolic disturbances associated with Cushing's syndrome, particularly hypertension, have normal contralateral adrenals and do not develop postoperative shock. Those patients whose major clinical manifestation is virilism and who have none of the metabolic disturbances associated with Cushing's syndrome constitute a good operative risk. Their contralateral adrenal is normal in size and apparently adequate in function since they do not tend to develop insufficiency following operation even in the absence of adequate preoperative preparation.

The worst operative risks are those patients with Cushing's syndrome where the adrenal cortical tumor is benign or if malignant has not penetrated the capsule. The patients with malignant tumors which have penetrated the capsule tend to survive the operative procedure, in part because the tumor is not actually completely eradicable. Enough functioning adrenal tumor tissue is left in the form of metastatic or local spread to prevent the development of acute adrenal insufficiency.

In determining, then, the probable operative risks the following factors must be considered. Patients with bilateral adrenal cortical hyperplasia constitute no undue risks except in so far as the actual operative technic is concerned. Patients who manifest the adrenogenital syndrome alone without any associated metabolic disturbances may be operated upon with a reasonable degree of safety. Those individuals who in addition to the adrenogenital syndrome also manifest evidences of Cushing's syndrome, particularly hypertension, constitute the worst operative hazards. This is especially true in the presence of a benign adrenal cortical tumor and to a somewhat lesser extent of a malignant neoplasm. All patients with adrenal cortical tumors, even those without Cushing's syndrome, should be prepared adequately preoperatively and properly treated postoperatively until all danger of adrenal insufficiency has disappeared.

Preparation of Patients for Operation.—There are no hard and fast rules for either preoperative preparation or postoperative therapy. Each case must be treated on its own merits and the extent and intensity of therapy is determined by the clinical picture that unfolds after the operation. In a general way the keynote for preparation is the liberal use of cortical extracts and salt both before the operation and afterwards until the patient is well out of danger. Preoperative preparation starts approximately twenty-four to forty-eight hours before the time scheduled for operation. Since the patient physiologically manufactures an excess of adrenal cortical extract, too vigorous preparation is not essential. Ten cc. of whole cortical extract and 10 mgm. of desoxycorticosterone are administered parenterally in 2 divided doses the day before operation. In addition 10 grams of supplementary salt are administered orally during the course of the day. On the morning of the day scheduled for operation a continuous intravenous drip of 5 per cent glucose in isotonic saline is started. This is continued throughout the operation and constantly thereafter until the patient is definitely past the stage where acute adrenal insufficiency may develop. In addition he receives 30 cc. of whole adrenal cortical extract intravenously and 20 cc. subcutaneously. In addition the patient should be given 50 to 100 mgms. of cortisone intramuscularly. Directly after the operation another 20 cc. of whole extract is given into the vein and 20 cc. is

with an average duration of five to seven years This period is probably somewhat less in patients with malignant adrenal cortical tumors

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comitantly with the ACTH in a dosage of 100 mgm. a day and is continued for a somewhat shorter period of time after the operation. These agents should be employed with caution and particular attention should be paid to the following: (1) the possible exacerbation of the diabetes, (2) the undue retention of fluids, and (3) the possible depletion and loss of excessive quantities of potassium.

Operative Technic.—Excellent operative technic descriptions are provided by Cahill and his group[3] and by Walters and Kepler. In general three different approaches have been used for removal of adrenal tumors: the extraperitoneal approach through the lumbar region, the transthoracic approach, and the transperitoneal route. Cahill[3] favors the transperitoneal approach through an oblique subcostal incision. With this method adequate exposure of the tumor is obtained and it is also possible to determine the presence and state of the opposite adrenal by palpation. Walters[77] favors a posterolumbar approach similar to that used in exposing the kidney. After the fascia of Gerota has been incised, the perirenal fat is reflected from the upper pole of the kidney and the kidney is retracted downward. This exposes the posterior aspect of the adrenal and it is possible to study it accurately from every side without disturbing the circulation. Broster and Vines[70] recommend the transthoracic route as the simplest approach in view of the fact that the adrenal vascular pedicle allows a slight range of upward movement. This technic has the serious disadvantage of creating an artificial pneumothorax.

In all except the transperitoneal route, exploration of both adrenals involves additional operative procedure. While with the postlumbar approach both exposures can be done at the same sitting, this is not true of the transthoracic approach. With this latter method, exploration of both adrenals involves a preliminary laparotomy, and only after recovery may the main operation then be performed.

Prognosis.—The prognosis is, of course, dependent on the nature of the underlying process and the results of treatment. The presence of an adrenogenital syndrome due to adrenal cortical hyperplasia or benign tumor is consistent with a normal life span—although perhaps a psychologically uncomfortable one—even in the absence of any specific therapy. Essentially the same is true of pseudohermaphroditism. The presence of a malignant tumor causing the adrenogenital syndrome, which unfortunately is usually the case, alters the outlook entirely by virtue of the malignant character of the adrenal neoplasm.

The presence of Cushing's syndrome alters the nonoperative prognosis. This is true in the absence as well as in the presence of adrenal tumors. These patients generally succumb to the ravages of the hypertension or to infections. Death occurs mainly as a result of cerebral vascular accidents, heart failure, coronary thrombosis, septicemia, or pneumonia.

Occasionally the disease will undergo a spontaneous remission. Such a case was described by Cushing.[6] The patient was apparently well twenty years after the initial hospital admission. But the general expectancy of the untreated patient with a true Cushing's syndrome is three to ten years

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Chapter 13

SYMPATHOGONIOMAS, NEUROBLASTOMAS, AND GANGLIONEUROMAS OF THE ADRENAL

Introduction.—Primary tumors of the adrenals may have their origin either in the cortical or medullary cells of the gland The adrenal cortex and medulla are in reality distinct organs with separate developmental histories As a matter of fact in some of the lower forms of life the cortical and medullary tissue are not fused but remain as separate organs The cortical tissue of the adrenal is derived from the mesoderm and is closely associated with the urogenital mass It is for this reason that adrenal cortical tumors so frequently and startingly affect the secondary sex characteristics The medullary tissue on the other hand is derived from the ectoderm and has a common origin with the cells constituting the sympathetic nervous system Certain cells of the celiac plexus migrate from the medial side of the cortical anlage of the adrenal into its center These cells are called sympathagones and they constitute the building cells of both the adrenal medulla and the sympathetic nervous system The sympathagones constitute therefore an early undifferentiated form of cell Further development of the sympathagones occurs along two lines They will give rise to a slightly more differentiated cell the sympathoblast on the one hand and the chromophiloblast on the other The sympathoblast will differentiate further into the neuroblast, and finally into a mature ganglion cell or sympathetic neuron while the chromaphiloblast will differentiate into the mature chromaphil cell

Since the sympathagone has its origin from the embryonic sympathetic nervous system the more differentiated cells derived from it are found wherever there is present sympathetic nervous tissue It is important to bear this in mind since tumors of these cells may have their origin not only in the adrenal medulla but in those various parts of the body where these cells develop Actually the chromaphil tissue consists of (1) The adrenal medulla (2) The paraganglia which are small round masses 1 to 3 millimeters in diameter found within or alongside the capsules of the ganglia of the sympathetic nervous system Usually a paraganglion is associated with each ganglion of the celiac renal adrenal aortic and hypogastric plexuses (3) A strip of chromaphil cells described by Kohn[1] situated ventral to the abdominal aorta and superior to the inferior mesenteric artery (4) The organs of Zuckerkandl[2] which lie on either side of the aorta at the origin of the inferior mesenteric artery These chromaphil bodies are quite large in the newborn measuring about 1 centimeter in length but rapidly degenerate and assume microscopic size at puberty (5) The carotoid glands which are situated at the bifurcation of the common carotoid artery one in each side of the neck

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dominant cell type the greater is the degree of malignancy. The sympathogoniomas are tumors which originate from the very immature sympathogone cells and hence are extremely malignant. They usually occur in intrauterine life or in earliest infancy and tend to metastasize rapidly, particularly to the retroperitoneal lymph nodes, to the liver and to the bony structure. These tumors are usually large, soft hemorrhagic growths, the cut surface of which shows necrotic and hemorrhagic areas. On microscopic section the tumor is apt to be very cellular and consists of small cells with small round nuclei surrounded by a narrow rim of cytoplasm. These cells are arranged in clusters or "rosettes" separated by strands or bundles of connective tissue which tend to lobulate the tumor.[7, 8]



FIG. 29.—Photomicrographic section of a neuroblastoma of the adrenal.

The cellular structure of the tumor will rarely consist exclusively of sympathogones but will frequently present the transitional stages in their development into neuroblasts, ganglion cells and even nerve fibers.

The Neuroblastomas.—In a general histologic sense there are two varieties of undifferentiated sympathetic nerve tumors which fall into the class of neuroblastomas. 1. The more undifferentiated tumors composed of small round cells with narrow rims of cytoplasm similar to but somewhat older than the cells constituting the sympathogoniomas and occurring in early childhood. These tumors correspond to the "sympathicoblastomas" of Bailey and Cushing.[21] 2. The more differentiated tumors composed of spindle cells or early nerve or unipolar cells with some fibers. These tumors

The various kinds of tumors which may arise from the adrenal medulla and from the sympathetic nervous system correspond to the various cell forms previously outlined

1 The sympathogonioma has its origin in the sympathogones and consists therefore of completely undifferentiated cells

2 The sympathoblastoma or neuroblastoma consists of a somewhat more mature and differentiated type of cell

3 The ganglioneuroma is a tumor composed chiefly of mature ganglion cells and nerve fibers

4 The chromaffinoblastoma consists of an undifferentiated type of cell the precursor of the chromaffin cell

5 The chromaffinoma consists predominantly of the chromaffin cells of the adrenal medulla

6 The paraganglioma consists of extra adrenal chromaffin cells having their origin in the paraganglia

Of the tumors just mentioned only the chromaffinomas and the paragangliomas yield the typical chromaffin staining reaction with potassium bichromate Extracts of these tumors since they are made up of chromaphil cells exercise pressor effects similar to that obtained with epinephrine [3,4,5,6]

In a broad sense then, we may divide the extracortical adrenal tumors into two large groups

1 Those in which the tumor cells yield the typical chromaffin staining reaction or are the precursors of these cells and these are

a) The chromaffinoblastomas
b) The chromaffinomas
c) The paragangliomas

2 The tumors made up of sympathetic nervous tissue These are

a) The sympathogoniomas
b) The neuroblastomas
c) The ganglioneuromas

It should be noted that this classification is in a sense artificial in that it presupposes a clear and always present clinical distinction as concerns the degree of cellular differentiation of the tumors In a strictly histologic sense the sympathogoniomas and the chromaffinoblastomas should consist exclusively of the most immature and undifferentiated cells the neuroblastomas of somewhat more mature and better differentiated cells, while the ganglioneuromas chromaffinomas and paragangliomas should consist of the most mature and most differentiated cells Actually the structure of the several tumors consists of cells of varying degrees of maturity and differentiation and in classifying a particular tumor we imply that the predominant cell of the tumor structure corresponds to that special category Emphasis is placed on this point because the literature is rich in confusion in the classification of the more immature sympathetic and adrenal medullary tumors, and thus overlapping of boundaries of degree of cellular maturity must be borne in mind

The Sympathogoniomas —In a general sense the degree of malignancy of the tumors outlined above is determined by the maturity of the predominant cell Thus the more undifferentiated and immature the pre

A third clinical group of neuroblastomas has been described in which there is an extreme anemia resembling the blood picture of pernicious anemia This group is referred to as the Lsser Herxig type [9] and is characterized by extensive bony metastasis Severe secondary anemia is usually seen in association with the Hutchinson tumors while moderate secondary anemia is not infrequently found in the Pepper group

General Signs and Symptoms and Clinical Course of Neuroblastomas —An excellent discussion of the clinical signs and symptoms observed in this disease is reported by Askin and Geschickter [11] They emphasize the frequency with which a non tender and non painful abdominal mass is observed This palpable mass may be in the region of the loin and represent the primary tumor or the palpable mass may be an enormously enlarged liver filling a considerable part of the abdomen Vomiting is a fairly common symptom as are periodic episodes of abdominal pain In addition the children frequently present a rather marked pallor some weight loss and fever Joint pains have been described but are rare A diffuse adenopathy occurs in about one fourth of the cases while a moderate leukocytosis occurs in about one half Where the tumor is primarily of the Pepper type the only findings may be emaciation pallor fever and enlargement of the abdomen due to the primary mass and the enlarged liver These cases occur in very young infants and usually pursue a rapidly fatal course In Askin and Geschickter s series [11] half of the patients died within a period of two to seven months after the onset of the symptoms Patients with the Hutchinson tumor lived somewhat longer Their signs and symptoms are different from those observed in the Pepper group Since the disease is characterized by extensive bony metastasis the presenting signs and symptoms are usually related to the metastatic lesions Hutchinson s clinical description of this group follows In the majority of cases the first thing noticed was some swelling about the bones of the skull which in several of them was ascribed to a fall or injury Following or sometimes preceding this proptosis of one or both eyes was observed In two-thirds of the cases discoloration of the eyelids on one or both sides is reported and in a few instances this was the first point to attract attention Anemia is a striking feature in all the cases the blood changes being those of a profound secondary anemia Leukocytosis has not been recorded in any case An abdominal tumor in one or the other loin was felt in only 5 of the cases Further progress of the disease is characterized by evidence of increased intracranial pressure with optic neuritis and blindness The progress of the disease in every instance has been rapid and the younger the patient the more rapid it appears

The roentgenographic studies reported by Askin and Geschickter[11] reveal the absence of x ray changes in the bony skeleton in instances of the Pepper group but extensive destructive processes in the bones of the patients afflicted with the Hutchinson tumor The parts most notably involved were the bones of the calvarium ribs clavicles and long bones

Treatment —The treatment of these cases is most unfortunately unsuccessful X ray and radiotherapy fail to alter the course of the disease although some shrinkage of the tumor perhaps occurs Surgical excision of the primary tumor is usually futile since metastasis occurs early and

usually occur in adults [9] and Bailey and Cushing [1] reserve the term "neuroblastomas" for these growths.

The neuroblastoma of the adult is extremely rare, usually small in size, and without much tendency to local invasiveness but tends to metastasize extensively, usually to the vertebra.

The more malignant neuroblastomas occur in early childhood.

The neuroblastomas of childhood are clinically roughly divided into two groups: 1 The Pepper and 2 the Hutchinson types, although considerable overlapping occurs [10,11]. Pepper[12] described a group of adrenal neuroblastomas characterized by appearance at an early age (three to eleven weeks) and frequently congenital. This group of tumors is highly malignant with extensive involvement of the liver in which nearly all the hepatic tissue is replaced by small tumor nodules. This marked involvement of the liver produces abdominal enlargement. There is usually no jaundice or clinically demonstrable ascites. The Hutchinson group of neuroblastomas[13] is characterized by metastasis to the skull, long bones, ribs, vertebra, sternum, dura and sometimes lungs and mediastinal lymph nodes. Clinically there is swelling of the skull, unilateral or bilateral exophthalmos with ecchymosis of the eyelids, increased intracranial pressure with choked-disc and frequently blindness, and a palpable abdominal tumor. The Hutchinson type of tumor is usually seen in an older age group of children than is the Pepper type. Scott, Oliver and Oliver[14] in an analysis of 162 cases of sympathetic tumors of the adrenal medulla found that the average age of the group of children afflicted with the Pepper tumor was 12.7 months while the average age of the Hutchinson group was 6.09 years.

The reason for the selective metastasis exhibited by the two groups of tumors is not clear. Frew[15] attempted to explain this difference in metastasis on the basis of the location of the primary tumor. He claimed that tumors of the right adrenal were of the Pepper type and that they tended to involve the liver and regional lymph nodes through lymphatic spread. The Hutchinson type involved the left adrenal and produced the skull and long bone metastasis through blood stream invasion. That this hypothesis is untenable is emphasized by the results reported by Scott, Oliver and Oliver[14]. Their conclusions were based upon an analysis of 158 instances of adrenal medullary tumors culled from the literature, of which 30 were of the Pepper and 38 of the Hutchinson type. Of the former group, 9 were primary in the right adrenal, 14 in the left, and 7 in both. Of the Hutchinson group, 18 were in the right adrenal and 17 in the left. Bruck[16] suggested that the extensive involvement of the liver in the Pepper group was due to a distribution of "rests" along the course of the veins which became simultaneously malignant. This hypothesis of "heterotopy" was subsequently adopted by Wilke[17], Shukovsky[18], Metzdorff[19] and Blumensaat[20].

In addition to the differences of metastatic spread of the two types of tumors, the Pepper tumor occurs at an earlier age, is considerably more malignant and runs a more rapidly fatal course. Its increase in malignancy is probably related to its early age of onset in that the cells comprising the tumor are even more immature and undifferentiated than those observed in the Hutchinson tumor.

In addition retroperitoneal lymphosarcoma is frequently associated with ascites and not unusually peripheral nodes may be available for biopsy which will reveal the true nature of the disease

3 Chloroma may produce exophthalmos and lesions in the bones of the orbit However this disease occurs in older children who present other clinical and hematologic evidences of leukemia In addition chloroma frequently produces tumors of the oral cavity and paranasal sinuses The chloromatous tumors are in general sensitive to *x* ray and radiotherapy

4 In the Hans Christian-Schuller syndrome large circular defects are produced in the skull and flat bones which may remotely resemble the metastatic skull lesions seen in the Hutchinson tumors However the former respond favorably to *x* ray therapy A biopsy will further clarify the clinical picture

5 A Ewing s sarcoma of the bone produces a fairly typical roentgenologic picture characterized by a periosteal reaction with splitting of the subperiosteal and cortical layers in onion peel fashion Skull metastasis in Ewing s sarcoma usually occurs late in the course of the disease Ewing s tumor like the previously mentioned clinical conditions which must be distinguished from a neuroblastoma responds very well to deep *x* ray therapy This point of radiosensitivity is extremely important in the differential diagnosis of neuroblastoma since there are few malignant neoplasms in childhood other than the sympathetic nerve tumors which are not sensitive to this form of treatment

Illustrative Cases

Case 1 —This first instance is a fairly classical example of a neuroblastoma of the Hutchinson type in a child of seven Although this patient presents all the features characteristic of this group there is in addition extensive hepatic metastasis The presence of extensive metastasis to the liver is in a strict sense more common in the Pepper variety but as indicated previously such overlapping not infrequently occurs

The patient was a colored boy seven years of age who was apparently well until four months prior to admission to the hospital At that time he began to develop pain in the left popliteal region There was no swelling or redness of the region involved although it was quite tender to touch There was some fever although the temperature did not exceed 101 F The pain was not severe and the child could move about with a fair degree of comfort One week later the left hip and buttock became involved in a similar fashion and during the course of the next two months the right knee wrist elbow and shoulder were afflicted in the mentioned sequence At no time was there any swelling or redness evident although tenderness was a constant feature The temperature remained elevated to approximately 101 F The local physician who treated the child assumed that he had rheumatic fever but the child failed to respond to the usual therapeutic measures During the month before admission to the hospital the child was bedridden There was a progressive loss of weight and strength and emaciation became quite marked Three weeks before admission a tender soft lump appeared on the back of the head One week before entry to the hospital the child became stuporous and continued this way until he died One day before admission to the hospital proptosis of both eyes developed

Physical examination of the child on the pediatric ward of the Mount Sinai Hospital revealed a limp stuporous wasted Negro boy of seven years of age There was a moth-eaten alopecia of the scalp There was marked separation of the coronal sutures of the scalp such separation measuring approxi

clinical evidence of such metastasis is almost always present at the time that medical help is sought. The early recognition of these growths is imperative if surgical intervention is to offer any hope of a successful cure. Such a case was reported by Lehman[27] who excised a typical adrenal neuroblastoma. The patient was reported well fifteen years later.[11]

Differential Diagnosis — There are 4 or 5 conditions with which neuroblastomas may be confused clinically.



Fig 30 — Metastatic destruction of the pelvic bones in a child with neuroblastoma of the adrenal

1 The most important of these is a Wilms tumor (embryoma of the kidney). However this tumor frequently produces renal symptoms with hematuria and positive pyelographic studies. Most important of all the embryomas of the kidney are highly sensitive to deep x-ray therapy in contrast to the irradiation resistant neuroblastomas.

2 Lymphosarcoma of the retroperitoneal nodes is equally responsive to x-ray therapy and thus can be distinguished from the neuroblastomas

physical examination of the heart suggested the existence of a congenital cardiac lesion The liver was palpable one and one-half fingers breadth below the costal margin and felt rather firm The spleen could not be felt The vulva was indurated and reddened and presented the picture of erysipelas The white blood cell count was 15 000 of which 52 per cent were polymorphonuclear leukocytes X ray of the chest skull and long bones showed no metastatic areas

Several days after admission to the hospital the child died At autopsy the left adrenal was found to be enlarged to the size of a walnut The tumor occupied the entire medullary space was firm in consistency and varied in color from a gravish pink to a dark red The medial edge of the tumor was delineated by normal appearing adrenal cortical tissue Actually the cortical tissue entirely surrounded the tumor although in its distal portion it was considerably thinned out The appearance was very much like that of a ball surrounded by a cover The right adrenal was normal The liver was somewhat enlarged and on section innumerable pearly gray depressed areas 2 to 8 millimeters in size were observed No evidence of metastasis was noted anywhere else in the body including the bony skeleton

The microscopic examination of the tumor showed that it consisted of nests clusters and rosettes of a fine fibrillar cytoplasm with indefinite cellular outlines Occasional polyhedral cells were seen The nuclei were essentially of two types There were small dark hyperchromatic nuclei and somewhat larger nuclei with a definite nuclear membrane fine chromatin network with 3 to 4 coarse chromatin lumps There were many gradations between these two well-defined forms The nuclei appeared in sheets and placques and the nests were surrounded by fibrous tissue The microscopy of the hepatic metastatic lesions was similar to that seen in the adrenals

These two patients differ in several respects The first patient may well be characterized as an instance of the Hutchinson variety of neuroblastoma since it occurred in an older child and was associated with extensive bony metastasis In the second patient an infant metastasis was essentially limited to the liver and hence falls into the group described by Pepper Of greater interest is the difference in microscopic structure between the two tumors The cells of the latter group were of a much more primitive character more highly malignant and approximated the histologic structure observed in the sympathogoniomas In the microscopic picture of the two tumors together are found almost all the gradations of the medullary cell development from the sympathogones to the ganglion cells

Ganglioneuromas —The ganglioneuromas are the most highly differentiated of the sympathetic nerve tumors They are composed chiefly of matured ganglion cells and medullated or non medullated nerve fibers They are usually benign small in size produce no symptoms and are found accidentally at autopsy They are usually found within the adrenal medullary substance but sometimes they arise from the sympathetic structures at the hilus and may occur anywhere along the course of the sympathetic nervous system Occasionally the primary ganglioneuroma may show some malignant areas consisting of undifferentiated cell forms When such malignant changes are present local invasiveness and metastasis may occur

The ganglioneuromas are exceedingly rare and most frequently occur in adults[23, 24] In Scott Oliver and Oliver s paper[14] six patients of the following ages are reported four four and one half, twenty two twenty-seven thirty seven and sixty five years

mately 1 centimeter in diameter In the occipital region of the calvarium a soft lump about 3 centimeters in diameter could be seen and palpated There was pitting edema of the forehead There was marked proptosis of both eyes, perhaps somewhat more pronounced on the right The lips and mucous membrane of the mouth were extremely pale The chest was terribly wasted The heart was not enlarged but there was a loud systolic murmur over the apex and a high pitched diastolic blow over the pulmonic area Examination of the abdomen revealed a huge hard liver, which extended to just below the level of the umbilicus Neurologic examination demonstrated the presence of a slight nuchal rigidity hyperactive knee kicks and ankle jerks, and a suggestive Kernig

Laboratory Data —The hemoglobin was 15 per cent while the white blood cell count was 20 400 A differential study showed the presence of 49 per cent granulocytes and 51 per cent lymphocytes Most of the red blood cells were achromic A few microcytes were in evidence but there were numerous normoblasts and a few megaloblasts There was considerable basophilic stippling The lumbar puncture yielded xanthochromic fluid clear but under increased pressure

Roentgen studies showed the presence of multiple minute areas of bone rarefaction throughout the entire cranial vault Similar changes were observed in both femora the right humerus and ribs The appearance according to the roentgenologist was that of multiple miliary metastases

Twenty four hours after admission to the hospital the child died At autopsy the liver was found to be extremely large weighing 1500 grams On section it was almost completely replaced with pinkish red metastatic growths In addition there were whitish metastatic lesions which consisted of strands compressing the lobules The spleen was grossly normal but the pancreas was large and the seat of extensive metastasis Here, too there appeared two kinds of metastatic lesions the red hemorrhagic soft areas resembling those seen in the liver and multiple one-centimeter white fibrous nodules resembling nerve fibers

The left adrenal appeared to be normal on gross examination The right adrenal however was pushed aside and almost replaced by a spherical growth the size of a baseball and weighing approximately 95 grams On section the mass was almost completely encapsulated by a fibrous growth similar in appearance to the whitish nodules previously mentioned in the pancreas In the center of the mass were 3 fairly well-defined red hemorrhagic areas

The kidneys testes and prostate were essentially normal The posterior mediastinal retroperitoneal and inguinal lymph nodes were enlarged and presented a metastatic appearance The ribs vertebræ skull and long bones were extensively involved in the metastatic process

The microscopic appearance of the right adrenal tumor showed two distinct structures The pale part was composed of nerve fiber tissue containing a small number of large polygonal or spherical cells apparently ganglion cell The dark part of the tumor consisted of oval cells with dark nuclei and a narrow rim of cytoplasm They were considerably larger than lymphocytes Occasional mitotic figures were seen The distribution of these cells was not equal In some areas they were massed in solid groups while in others they were present singly and isolated No definite rosette formation was observed Microscopic aggregations of tumor cells were found in the left adrenal spleen and lungs

Case 2 —The clinical and pathologic picture of this second case is quite different The patient was a six month old white female baby who was well until one week before admission to the hospital when she developed fever and cough Twenty four hours before entry into the hospital slight redness was noted over the vulva and pubis and the temperature rose to 105 F On physical examination in the hospital the child was found to be markedly cyanotic and tachypneic The heart was enlarged both to the right and to the left and there was a marked systolic blow over the pulmonic area The

Chapter 14

PHEOCHROMOCYTOMA AND PARAGANGLIOMA OF THE ADRENAL

THE CHROMAFFIN TUMORS

Introduction —The chromaffin tumors may arise either from the medullary tissue of the adrenal or from chromaffin tissue located elsewhere in the body. As previously mentioned this extra adrenal chromaphil tissue may be located in the paraganglia which lie within or alongside the capsules of the ganglia of the sympathetic nervous system or in a strip of chromaphil tissue ventral to the abdominal aorta and superior to the inferior mesenteric artery or in the organ of Zuckerkandl on either side of the aorta at the origin of the inferior mesenteric artery and finally in the carotid glands. The coccygeal body has been variously described as part of the chromaffin system but since it does not give the typical chromaffin staining reaction it probably does not fall into this group.[1] It is important to bear this diffuseness in mind if we are to avoid the error of unsuccessful treatment in looking to the adrenals only as a source of the tumor in patients presenting the typical syndrome. These tumors may be located anywhere in the abdomen in the neck and even in the chest.

Chromaphil tissue in general yields a typical staining reaction with chromic salts. This is one of the distinguishing features of these cells and of the tumors. Stilling[2] and Kohn[3] devised the method for staining this tissue by exposing it to a solution of potassium bichromate washing and examining the sections grossly for brownish patches. Wiesel[4] modified this technic somewhat by staining the tissue with bichromate and fixing it in 10 per cent formalin. The tissue is then washed and bleached by placing it in sunlight in hydrogen peroxide for six to twenty four hours. The chromaphil cells thus stand out in sharp brown contrast against the bleached background. The chromaffin reaction is chemically a reduction phenomenon and as shown by Ogata and Ogata[6] is due to the presence of a strong reducing substance probably adrenalin.

Tumors of the chromaffin tissue have been variously referred to as chromaffin cell tumors pheochromocytomas and paragangliomas. The last term was originally introduced by Alezais and Peyron[7] to designate the extra adrenal chromaffin tumors arising in the paraganglia. In the literature however these various terms are used synonymously.

Incidence —Pheochromocytomas are rare tumors. In 1929 Rabin[8] reviewed the literature carefully and found 30 authentic instances of chromaffin tumors of the adrenal medulla although extraadrenal tumors of this character particularly of the carotid bodies were more common. In 1932 Eisenberg and Wallerstein[9] found that the total

Such an instance was recently observed at the Mount Sinai Hospital The patient was a sixty five year old white male who was admitted because of an adenocarcinoma of the prostate Following a suprapubic prostatectomy the patient died At autopsy the adrenals appeared to be grossly normal On microscopic examination however several small nodules of whorled neural fibers containing ganglion cells were found in the medulla of the right adrenal In addition the medulla was infiltrated with small round cell histiocytes and plasma cells

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blue with hematoxylin These cells are comparatively rare After fixation with chromic salts, the cytoplasm of some of the cells stains yellowish-brown This reduction of the chromic salts occurs independently of the cytoplasmic granules since the yellow brown color is present between the

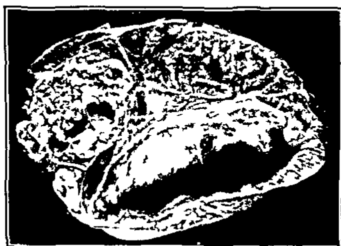


Fig 31 —Hemisection of a pheochromocytoma of the right adrenal The tumor was the size of a large honey dew melon and weighed 2000 grams Note the hemorrhagic cystic degeneration

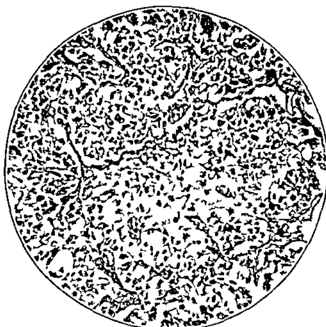


Fig 32 —High power microscopic section of an adrenal pheochromocytoma removed at operation

number of cases of adrenal medullary pheochromocytomas reported in the literature had increased to 53 and by 1937 Wells and Boman[27] had found 82 such cases in the literature. By 1939 8 additional cases had been reported.[40] More recently Smithwick[67] has collected 270 cases from the literature, 33 per cent proven at operation and 67 per cent at autopsy.

Berdez[10] in 1892 reported a medullary tumor of the right suprarenal gland. This tumor was vascular and encapsulated and was probably a pheochromocytoma. One year later Manasse[11] reported an adrenal medullary tumor which had the definite histologic characteristics of a chromaffin cell tumor. This was really the first well-defined and histologically clear instance of such a tumor. In 1904 Marchetti[12] described a bilateral pheochromocytoma of the suprarenals. That this is not uncommon is attested to by the fact that of the group of 90 cases reviewed by Brunschwig and Humphreys[40] 17 or approximately 19 per cent were bilateral. The clinical significance of this observation is evident. The concomitant presence of pheochromocytomas and other neoplasms has been commented upon[9] but the only significant association is with the neurofibromata. Suzucki[13] was the first to report the simultaneous presence of these two diseases, and since this original report 8 more such instances have been recorded.[14, 15, 16, 17, 41, 4] It is curious that with the exception of one of these instances[4] none of the other cases manifested the symptoms of medullary hyperadrenalism.

The first inkling that these curious tumors of the adrenal medulla were capable of producing clinical symptoms is contained in a report by Neusser and Wiesel[18] on a case of Kolisko's which showed marked vasomotor instability. Three years later Helly[19] reported a case with hypertension and glycosuria, and in 1922 L'Abbe, Tinel and Doumer[20] observed a case with paroxysmal hypertension. Since these original reports the clinical syndrome associated with the pheochromocytomas has become well-defined and will be elaborated upon later.

Pathology of the Pheochromocytomas.—These tumors may be benign or malignant although the largest percentage of cases are benign. Of the 53 instances of this medullary tumor collected from the literature and reported by Eisenberg and Wallenstein[9] there were 5 cases of malignancy.[1, 3, 24, 5] In each of these latter instances the malignant tumors were bilateral involving each adrenal. The malignant chromaffin cell carcinomata tend to metastasize early and extensively. Frequently the malignant tumors do not produce hypertension.

The benign tumors may be solid or cystic and vary in size from 1 to 12.5 centimeters. Usually the tumors are fairly small and encapsulated and of a mottled yellow brown color. The cystic tumors are hemorrhagic and contain many necrotic areas. The benign tumors show no tendency to invade either the medulla or the cortex but rather to compress these areas which are well demarcated from the mass by a rather thick capsule.

The benign pheochromocytomas are highly cellular tumors consisting of islands of large polyhedral cells which are markedly irregular in shape and vary in size from 15 to 45 microns in diameter. The cytoplasm is abundant and finely granular in character and stains a bluish red with hematoxylin eosin. Some of the cells however are markedly basophilic and stain deeply

More recently nor-epinephrine has been demonstrated to be present not only in the normal adrenal medulla but also in pheochromocytomas

The Clinical Picture of Pheochromocytoma —The classical clinical picture of pheochromocytoma is characterized by periodic episodes of paroxysmal hypertension cardiac palpitation severe anxiety and tremulousness headache vomiting glycosuria and vasomotor phenomena The identity of this picture with that induced by an injection of a fairly large dose of adrenalin is evident

The disease is encountered mostly between the ages of twenty and forty years although Howard and Barker[39] in their analysis of 18 cases from the literature report one instance in a boy of eighteen and one in a man of sixty nine The author has observed a case of extra adrenal paraganglioma in a male child of seven years of age The reported cases are about equally divided between males and females

In the excellent and comprehensive analysis of the cases reported by Howard and Barker[39] the duration of the symptoms varied from several months to eleven years before the disease was recognized clinically or discovered during necropsy studies The character of the symptoms which the patient develops is alarming enough to cause him to seek the aid of a physician but until fairly recently the medical profession had not been adequately alert to the possibility of this clinical entity and many patients were considered as instances of anxiety episodes or hypertension associated with cardiovascular or renal disease

The frequency of the attacks varies considerably Early in the course of the illness weeks or months may elapse between attacks As the disease progresses however episodes may occur daily or even several times a day The factors which may precipitate paroxysms are variable Emotional upsets undue physical effort heavy meals prolonged fasting manual manipulation of the tumor unusual positions of the body in which the tumor is automatically compressed are frequent causes of paroxysms However episodes often occur in the absence of these provocative factors The duration of the individual attack varies greatly The average duration is approximately one to two hours although they may be as short as three minutes and as long as sixteen hours[39]

The symptoms which usher in and are associated with the attack differ widely In almost all instances uncontrollable fear and anxiety are immediately evident There is severe cardiac palpitation profuse sweating pallor and cyanosis of the skin and frequently pallor alternating with flushing of the skin of the face There occurs an increase in the respiratory rate dyspnea and a marked acceleration of the pulse In about 20 per cent of the cases reported bradycardia was noted during the attack Spontaneous nausea and vomiting almost always occur particularly if the attack follows directly after a meal There is usually severe headache generally occipital but frequently involving the entire head In addition many of the patients complain of severe precordial pain epigastric pain and cramp-like pains in the extremities There is marked urinary frequency Very rarely however urinary suppression occurs

A high percentage of patients with pheochromocytoma complain of excessive sweating This was found in 9 out of 10 cases in Smithwick's

granules also in the nuclei and nucleoli. This would suggest that the substance which reduces the chromic salts, and which is probably adrenalin or nor-adrenalin, is secreted by some of the cells but by no means all and then inundates the cell involved. The nuclei of the cells are as irregular in size and shape as are the cells themselves. They may be round, oval, flattened, triangular, or simply irregular, and contain one or more well defined nucleoli. Within the cytoplasm of the cells and also between the cells hyaline inclusion bodies are frequently seen. These vary considerably in size, are usually spherical or ovoid, stain deeply with eosin, and are unaffected by chromic salts. Scattered among the typical tumor cells are occasional isolated extraordinarily large ovoid cells with a pale, clear cytoplasm and a centrally placed, deeply staining nucleus. These cells do not show the characteristic chromic reaction. The tumor is highly vascular and the islands of the cells are separated by numerous capillaries and fine strands of connective tissue. It is interesting that in several instances tumor cells have been found within the blood vessels of the tumor. The tumor in general shows many small hemorrhagic areas, areas of vacuolar degeneration and necrosis. According to Rabin[8] and Geschickter,[6] there is an absence of fat, lipoids, glycogen, and iron in the tumor cells. In somewhat less than 20 per cent these tumors may be bilateral.

Pharmacology of Pheochromocytomas.—Since these tumors, whether adrenal or extra-adrenal in origin, are made up of cells identical with those of the adrenal medulla, it was reasonable to suspect that they were capable of secreting adrenalin. When the clinical picture of this disease was more clearly defined, the similarity between the symptomatology associated with these tumors and the pharmacologic actions of adrenalin became quite obvious. That these tumors are actively secretory was demonstrated by the microscopic studies of Ogata and Ogata.[7] These authors showed that chromium salts are precipitated in the tissue by the presence of a strong reducing substance, probably adrenalin. There are at least 13 reported instances in the literature in which extraction studies of the tumor tissue were conducted.[8,18,9,30,31,33,34,36,37] In all the instances, with the exception of one, the presence of a pressor substance identical in pharmacologic effects with that of adrenalin was demonstrated. In the one equivocal result reported by Biskind, Meyer, and Beadner[37] the presence of other substances, probably catechols, interfered with the quantitative test for adrenalin. However, extracts of this tumor produced marked mydriasis of the cat's eye. Kelly and his coworkers[35] succeeded in recovering epinephrine in crystalline form from the tumor of their patient. In several cases quantitative studies were carried out, and the total amount of adrenalin present in the respective tumors varied from 6.7 to 1200 milligrams.[4] The significance of this is emphasized if we bear in mind that the average amount of epinephrine recoverable from both adrenal glands in the human is about 8 milligrams.[38]

The methods employed for both the qualitative and the quantitative determination of adrenalin left much to be desired. Nevertheless, the conclusion that the secretory product of the pheochromocytoma is epinephrine seems inescapable.

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series[67] and in 52 per cent of the case reports he reviewed. The sweating is not due to the epinephrine *per se* but is due to a reflex parasympathetic discharge to maintain homeostasis as regards body temperature. This phenomenon is rare in ordinary hypertensive patients.

Evidence of severe peripheral vasospastic phenomena are frequent in patients with pheochromocytomas, and their presence in a hypertensive should lead one to suspect such an underlying etiology.

Unexplained mild elevations of body temperature (over 1° F) are not unusual in these patients. During the paroxysms the temperature may rise to 105° F. These phenomena are related to the interference with heat elimination as the result of vasospasm and are but rarely noted in essential hypertension.

Postural hypotension and postural tachycardia occur frequently in patients with pheochromocytoma, especially those with persistent hypertension, as opposed to the low incidence of these findings in patients with essential hypertension. These findings in the former group undoubtedly represent alterations in splanchnic and muscular vasodilatation of humoral origin taking precedence over normal vasoconstrictor mechanisms involved in assuming the upright position.

The most marked finding on physical examination is, of course, the precipitate elevation of both the systolic and diastolic blood pressure. Beginning at normal levels before the attack, with the paroxysm the systolic blood pressure usually exceeds 200 millimeters of mercury, frequently rises to over 250, and occasionally exceeds 300. The diastolic pressure varies proportionately. With the sudden marked elevation of the blood pressure there generally occurs a pronounced distention and engorgement of the neck veins, and frequently a considerable increase in the circumference of the neck. Pulmonary edema occurred in about one half the cases reported by Howard and Barker.[39]

A normal response to the cold pressor test is common in patients with pheochromocytoma but unusual in patients with essential hypertension.

During the paroxysm hyperglycemia and glycosuria are observed in approximately one half the patients. This is due to the glycogenolysis engendered by the outpouring of adrenalin and when present constitutes an important diagnostic aid.

Furthermore, fasting blood sugars were elevated in 61 per cent of the cases reviewed by Smithwick[67] in both paroxysmal and non-paroxysmal types. Permanent diabetes has been noted in patients with pheochromocytoma,[69, 74] but following removal of the tumor carbohydrate tolerance returned to normal. It is possible, of course, that in these cases the mechanism of the elevation of blood sugar may be increased elaboration of adrenal cortical hormones rather than only hepatic glycogenolysis.

Electrocardiographic tracings during the attack are very variable and not particularly significant. There may be no alteration other than an increase in heart rate. Occasionally short runs of auricular or ventricular tachycardia or ventricular extrasystoles are observed. Alterations in the T waves during the episodes are not striking, although marked elevation in the T wave in all leads has been reported in one instance.[39]

In patients in whom the disease has been present for a considerable period of time or in those instances with a persistent hypertension extensive eyeground changes can occur Narrowing and nicking of the blood vessels with exudates and hemorrhages have been observed The fundal changes in these patients are similar to those seen in any group with severe and prolonged hypertension The tendency to eyeground changes is much more pronounced in those patients with a persistent hypertension than in those who develop elevation of the blood pressure only during attacks In Howard and Barker's analysis[39] of 18 cases definite fundal changes were *observed in 7 instances Six of these cases had a persistent hypertension*

Similarly enlargement of the heart is determined not so much by the height that the blood pressure attains as by the duration of the hypertension Where this feature has become a permanent part of the clinical picture cardiac enlargement is almost always present

In approximately 50 per cent of the cases a mass can be palpated in the abdomen The palpable mass may not be the tumor itself but rather a kidney or the liver pushed down by the tumor Where the palpable mass is actually tumor tissue manipulation of the growth may result in the precipitation of an attack

The routine laboratory findings in this disease are not especially significant The blood count and differential studies are essentially normal The urine may occasionally show some albumin and casts and during the paroxysms of hypertension sugar Where the hypertension has persisted for a considerable time impairment of renal function with fixed specific gravity and elevation of the blood non protein nitrogen may follow

The basal metabolic rate was elevated in approximately half of 35 cases in which it was determined[67] This type of hypermetabolism Smithwick states is refractory to thyroidectomy and the action of antithyroid drugs Inasmuch as an elevated basal metabolic rate over plus 20 per cent is encountered in only 5 per cent of patients with essential hypertension the possible presence of a pheochromocytoma must be excluded in a patient with hypertension and an elevated basal metabolism

Diagnosis —The diagnosis of this disease is dependent to a considerable extent upon the awareness of the physician to the existence of this clinical entity It must be remembered that the location of the pheochromocytoma or paraganglioma is not limited to the adrenals These tumors may be found in any part of the body Where the classical clinical picture is present its recognition is relatively easy However there are considerable variations in the syndrome Hypertension may not be paroxysmal in character but rather permanent These cases are frequently overlooked as instances of hypertension with or without renal disease[43–48] In a careful analysis of the histories of the patients in this group the fact can frequently be elicited that previous to the development of a persistent hypertension elevations in blood pressure occurred paroxysmally When the patient comes under observation with a persistent hypertension the usual clinical picture of pheochromocytoma is lacking The characteristic episodes of anxiety tremulousness vasomotor instability *etc* are not observed Occasionally transient glycosuria is noted and frequently an increase in the basal metabolic rate The diagnosis of hyperadrenalism under these circum

stances is quite difficult and is dependent upon the index of suspicion of the physician and the use of the more mechanical methods of diagnosis such as x-rays of the abdomen, intravenous pyelography, and perirenal insufflation. Where the tumor is extra-adrenal in origin and associated with a permanent hypertension, the diagnosis is practically never made unless the patient is operated upon for relief of the hypertension and the tumor is thus accidentally observed.

For more than one reason, all patients with hypertension, whether paroxysmal or permanent in character, are entitled to a flat plate of the abdomen and to intravenous pyelographic studies. Where the hyperadrenalism is due to a medullary tumor of the abdomen, such studies would reveal its presence in approximately two thirds of the cases.[39]

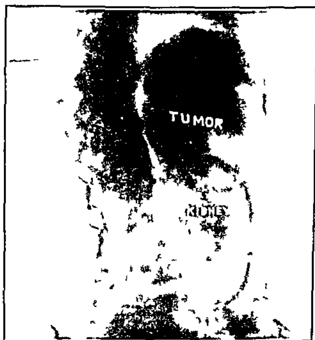


Fig. 33.—A case of severe paroxysmal hypertension. Large adrenal tumor (pheochromocytoma). Note well defined fascial envelope (Gerota's fascia). Oblique view. (Mencher, courtesy of Jour. Am. Med. Assn.)

If the pyelographic studies fail to reveal any abnormalities, the use of perirenal insufflation with air or oxygen has been suggested.[49,50,58] This procedure has proved to be quite effective,[49,59] although several severe reactions and some deaths from air embolism have been reported.[50,5] Since the use of oxygen for perirenal insufflation no further fatalities have been recorded. In our own experience at the Mount Sinai Hospital, where over 200 perirenal insufflations with oxygen have been performed, the procedure has proved of invaluable aid in the diagnosis of both cortical and medullary tumors. In this series there have been no fatalities and no incidence of undue reactions other than that of pain in the shoulder due to irritation of the diaphragmatic leaves by the injected oxygen.

When patients are observed between episodes, it may be desirable to initiate an attack in order to establish the diagnosis and perhaps to localize the tumor to the proper side. The attacks always constitute a hazard to the patient and must be approached with a great deal of caution. Procedures to initiate paroxysms should be employed only when absolutely essential. Gentle massage to one side or the other of the abdomen will occasionally precipitate a paroxysm and will thus also define the location of the tumor. Such massage will elicit the desired result only if the tumor is fairly large, perhaps palpable, and located in the adrenal. Occasionally starvation for from twelve to twenty-four hours will induce an attack. Coller, Field and Durant[43] have suggested the subcutaneous injection of epinephrine to precipitate an episode, while Nuzum and Walton[54] have obtained successful results by applying pressure over the carotid sinus.

Roth and Kvale[70, 71] suggested the intravenous injection of histamine to induce an attack in suspected cases. 0.05 mgm. of histamine base is injected intravenously and in the presence of a pheochromocytoma a marked increase in blood pressure and a characteristic attack promptly occurs, usually within two minutes. In normal individuals, in patients with hypertension as well as in those individuals who are hyperreactive to the cold pressor test, the increase in the systolic blood pressure following the intravenous administration of histamine is slight, generally not exceeding 6 to 12 mm. of mercury. In patients with pheochromocytomas studied by these investigators, the systolic blood pressure rose from 110 to 132 millimeters of mercury to over 240 mm. of mercury, while the diastolic pressure rose from 68 to 85 to 142 to 146 millimeters of mercury. After the successful removal of the tumor the histamine response becomes normal.

Dibenamine in moderate dosage is chiefly adrenolytic, but in sufficient dosage is sympatholytic as well and antagonizes the action of nor-epinephrine as well as that of epinephrine. Dibenamine blocks only the excitatory action of these drugs and not the inhibitory effects. It does not, however, prevent the action of epinephrine on the heart. In most normal individuals the administration of dibenamine results in a slight fall in blood pressure, while in patients with moderate essential hypertension this drug often induces a modest postural hypotension. No depressor response is noted in patients with malignant hypertension. In testing a patient with hypertension for the presence of an underlying pheochromocytoma, dibenamine is administered intravenously in a dose of 7.0 mgm. per kilogram of body weight in 300 cc. of 5 per cent glucose in normal saline over a period of an hour. A significant decrease in blood pressure ensues in patients with pheochromocytoma.[75] The dehydrogenated ergot alkaloids (dihydroergocornine, dihydroergotamine) inhibit both the inhibitory as well as the excitatory effects of epinephrine but as yet have not been reported as being employed in patients with pheochromocytoma. Goldenberg and his co-workers[76] reported that benzodioxan derivatives (933F, 2[1-piperidylmethyl]-1,4-benzodioxan, and 1164F, [2-(4-dimethyl)] piperidyl methyl benzodioxan) given intravenously resulted in significant falls in blood pressure in patients with persistent hypertension due to pheochromocytoma. This is in contrast to the lack of response in patients with essential hypertension.[64] However, Taliaferro[73] and her associates reported one instance in which a

patient with presumed essential hypertension responded in a fashion similar to a patient with a pheochromocytoma.

The technic of performing this test is as follows. During a period of hypertension 10 to 15 mgm. of benzodioxane (933F) is given intravenously over a two-minute period. Blood pressure readings are taken at frequent intervals prior, during and after the administration of the drug. If the hypertension is due to a pheochromocytoma, a fall of the blood pressure of up to 50 to 70 millimeters of mercury is noted. The blood pressure returns to its former level in about fifteen minutes. Side actions include tachycardia, flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing respiration and dizziness.

In patients with this disorder tetraethylammonium will frequently[79] but not invariably induce a paroxysmal hypertensive attack. It is administered in a dosage of 400 mgm. intravenously. Whereas in the ordinary essential hypertensive there is a marked fall in blood pressure following the procedure and in the normal subject there may result a mild hypotensive effect, in the patient with a pheochromocytoma, hypertension is induced. This paroxysm lasts longer than a similar one induced by histamine. The hypertension, however, may be promptly controlled by placing the patient in the erect position. Roth and Kvale have obtained both false negative and false positive results with this test, and Bartels has had a false negative result in a proven case of pheochromocytoma.

Mecholyl in doses of 25 mgm. subcutaneously may induce a hypertensive attack in patients with this type of adrenal tumor. Guarneri and Evans[7] claim this test to be more accurate than the histamine test.

In a case of pheochromocytoma and diabetes mellitus Goldner[71] has reported the insulin tolerance test to be a successful method of inducing a paroxysmal attack.

In general, then, in a patient with normal blood pressure who is suspected of having a pheochromocytoma, histamine, mecholyl, or tetraethylammonium, preferably all three, may be employed to induce a paroxysm. If persistent hypertension is present, benzodioxane or dibenamine may be employed to rule out a pheochromocytoma as the underlying etiologic agent.[70 78 79 80]

Where the clinical picture is strongly suggestive, even in the absence of corroborative laboratory data, surgical exploration is indicated. It is worth repeating once more that chromaffin tumors are frequently extra-adrenal, and when surgery is decided upon this fact must be borne in mind.

Differential Diagnosis. — The complete classical picture of hyperadrenalism is simulated by no other clinical condition. Loosely resembling episodes are, however, sometimes observed in tabetic crises, lead poisoning and mediastinal tumors with vagus irritation. In these instances there may occur an intermittent elevation of the blood pressure, but the general picture is readily distinguishable from that of pheochromocytoma. Penfield[55] described a rare type of "autonomic diencephalic fit" which resembles hyperadrenalism and which may be confused with it. In the case reported by Penfield the patient presented paroxysmal episodes characterized by restlessness, severe headache, vasomotor phenomena, marked diaphoresis, dilatation or contraction of the pupils, increase in pulse rate, and consider

able elevation of the blood pressure At necropsy a tumor of the third ventricle was found which pressed on the thalamus symmetrically on both sides However during life this patient presented many physical signs pointing to the intracranial origin of the symptoms

A syndrome of "diencephalic hypertension" occurring in patients without intracranial tumor has been described by Page[69] and studied more recently by Schroeder and Goldman[81] The patient is usually female a hypertensive, with a markedly labile blood pressure There is noted a periodic blotchy blush over the face and upper chest and beads of perspiration over this area Tachycardia lacrimation and hyperperistal is are frequent The abnormalities are those of emotional autonomic and vasomotor instability The intradermal administration of 0 25 mg of histamine will frequently reproduce the syndrome Smithwick claims that in this group all the patients are hyperreactors to cold and respond well to splanchnicectomy

Occasionally hyperadrenalism may be characterized by convulsive episodes Other causes of convulsive seizures are readily distinguished from those of pheochromocytoma in that the former fail to show the additional attendant phenomena associated with the latter

Hypertension occasionally of a varied type is seen in tumors of the adrenal cortex These cases however are associated with signs of masculinization and virilism or evidences of Cushing syndrome which are totally lacking in instances of chromaffin cell tumors Biochemical assays for the neutral 17 ketosteroids the excretion of which is usually increased in adrenal cortical tumors further serve to differentiate the two groups

Finally pheochromocytoma with persistent hypertension will readily simulate the usual malignant hypertension associated with cardiovascular and renal disease Patients who have suffered with hyperadrenalism for a prolonged period of time with or without persistent hypertension may develop marked impairment of renal function with albuminuria and casts The fundi will show the changes observed in malignant hypertension The heart may be enlarged and there may be evidences of heart failure These cases can be distinguished from those of malignant hypertension only by eliciting a thorough and painstaking history in which the previous paroxysmal character of the hypertension is brought to light and by the use of the benzodioxane test In addition the routine use of x rays of the abdomen pyelographic studies and perirenal insufflation will aid in uncovering the presence of an adrenal medullary tumor

Prognosis —The ultimate prognosis is dependent upon the prompt recognition of the disease and the surgical removal of the tumor Cases of unoperated pheochromocytoma may run a prolonged course of many years duration Death may follow through cerebral hemorrhage pulmonary edema uremia coronary occlusion and frequently death may occur suddenly for no well-defined reason These patients are notoriously poor surgical risks Minor operative procedures may precipitate the patient into severe shock with a fatal outcome[27]

Although the paroxysmal episodes may originally be relatively mild as time elapses the frequency and intensity of the attacks steadily increases so that the patient is completely invalided The successful surgical re

moval of the tumor results in a complete cure with relief of all the symptoms and disappearance of the hypertension. Even in patients with a persistent hypertension operation has resulted in a marked decrease in the blood pressure, frequently to normal levels, regression of the fundal changes, and improvement in the cardiovascular and renal status.[43]

Treatment.—The paroxysmal episodes, particularly those of short duration, may be relieved by the inhalation of amyl nitrite.[3, 5, 56] It has been suggested that in view of the peripheral vasodilator action of the nitrites their daily use in divided doses may control the frequency and intensity of the attacks. However, the few scant reports in the literature concerning the daily use of sodium nitrite have not been encouraging.[5, 57]

Dibenamine may be employed in the preparation of the patient for surgery. This drug will prevent paroxysmal hypertension during the operation. It is given intravenously by slow drip in 300 to 500 cc of normal saline or 5 per cent glucose over a period of an hour. The dosage is 4 to 6 mgm per kilogram of body weight, but the total should not exceed 500 mgm.

More recently we have successfully employed priscoline for the operative preparation of these patients. It is given by slow continuous intravenous drip starting a short time before operation and continued until the tumor is removed. The solution contains 5 mgm of priscoline in each 100 cc of normal saline and is administered at the rate of 25 to 30 drops per minute or 5 mgm per hour.

In an analysis of 20 operated cases gathered from the literature and reported by MacKenzie and McEachern,[5] 15 recovered completely and have remained free from attacks while 5 died as a direct result of the operative procedure. Two of the deaths were due to shock and occurred in three and six hours after operation, 2 patients died in coma with hyperpyrexia within forty-eight hours, and 1 patient died of a bronchopneumonia. Of the 20 patients that were operated upon 9 actually developed moderate to severe collapse and shock. Seven of these patients recovered. When shock occurred it usually occurred during or directly after the operation, and in those patients who recovered the manifestations of shock disappeared within twenty-four hours. The explanation of the marked susceptibility to operative shock on the part of these patients is not entirely clear. It has been suggested that due to the excessive formation of adrenalin by the tumor there occurs a compensatory physiologic atrophy on the part of the normal medullary tissue, and the sudden removal of the tumor with its excessive epinephrine content results in collapse. This may in part be true, but shock is frequently observed in these patients following any operative procedure in which the tumor is in no way affected. Similarly, it is difficult to believe that these patients have any adrenal cortical deficiency, since they show no evidence prior to operation of overt cortical underfunction. Still the picture of shock observed in patients with pheochromocytoma is qualitatively identical with, although by no means as frequently fatal as, that observed in patients with adrenal cortical tumors who are operated upon. In all probability certain adrenal cortical and medullary functions of at present an intangible character and not yet subject to laboratory definition are dis-

turbed in both groups of patients One possibility that must be borne in mind is that the constant liberation of epinephrine results in a continuous secretion of adrenocorticotropin and consequent adrenal cortical over activity When the tumor is removed the removal of the stimulus for adrenocorticotropin secretion may induce a temporary decrease of adrenal cortical function In any event until we learn considerably more about these functions the patients must be prepared for operation with the intelligent use of the agents available to us

The operative approach will depend on the location of the tumor If there is a single tumor limited to one adrenal extra peritoneal approach by lumbar incision will be the procedure of choice Where the location of the tumor has not been determined a transperitoneal approach through a mid line ventral incision is indicated in order to explore adequately the paraganglia chains Lateral extension of the incision will permit also of adequate exploration of both adrenals The transperitoneal approach is somewhat more extensive and more difficult than a simple lumbar incision but may save the patient a further operation The additional surgical risk is well justified in uncertain cases

The anesthesia of choice should be one that is associated with the least drop in blood pressure Spinal anesthesia should be avoided Ether and gas-oxygen are well tolerated as is avertin

Before the patient is operated upon all preparations should be made for blood or plasma transfusions and intravenous 5 per cent glucose in isotonic saline An adequate supply of adrenalin and whole cortical extract must be available for immediate use A sudden considerable rise in blood pressure during the operation is an indication for temporary cessation of the operation until the blood pressure returns to the preoperative level The use of amyl nitrite inhalation through the anesthesia mask will help in the reduction of the hypertension A severe fall in the blood pressure to shock levels calls for discontinuance of the procedure Manipulation of the tumor is to be avoided as much as possible while the surgery should be rapid and gentle

When collapse develops it usually occurs during and directly after the operation This should be countered with prompt transfusion of plasma or whole blood repeated as necessary A continuous intravenous drip of glucose in isotonic saline should be started directly before the operation and continued for a prolonged period after In the presence of shock adrenalin must be administered intravenously and subcutaneously and adrenalin in-oil intramuscularly The epinephrine will cause a prompt although temporary rise in blood pressure and its use through the various channels particularly adrenalin in-oil intramuscularly should be continued at intervals until the patient is out of shock At the first signs of collapse whole adrenal cortical extract should be administered intravenously and continued at frequent intervals both intravenously and subcutaneously until the patient is well out of danger With the administration of blood transfusions and intravenous fluids the use of adrenal cortical extracts predisposes somewhat to the development of pulmonary edema This should be looked for carefully and at the first sign of the accumulation of moisture in the lungs all therapy should be discontinued In general in

this group of patients when the use of adrenal cortical extracts is decided upon whole extract may be used with greater safety and advantage than desoxycorticosterone acetate The former predisposes less to pulmonary edema and probably provides factors other than those concerned with electrolyte control The lack of these ill-defined factors may play some role in the development of the operative shock

X ray therapy is ineffective in the treatment of pheochromocytoma although one instance has been reported with temporary relief of attacks This patient was symptom free for a period of several months but the attacks subsequently recurred and the patient died during one of them[60 61]

Illustrative Representative Cases

The following case record from our wards was reported previously in detail by Beer King and Prinzmetal[62] The patient was a young woman of twenty six who was admitted to the medical service of the hospital with the following history Nine years previously she had first noted the insidious onset of occasional episodes characterized by fatigue throbbing headache and sweats These symptoms were attributed to hyperthyroidism but following a subtotal thyroidectomy her symptoms continued unabated The histologic diagnosis of the removed thyroid tissue was that of adrenocarcinoma The microscopic sections were subsequently reviewed by the pathologist at this hospital who corroborated the original diagnosis

The symptoms became progressively more severe and in addition seven years before admission to our hospital she noted that the distal phalanx of the right index finger would on occasion become perfectly white change to a deeply cyanotic hue which in turn would be replaced by a dusky red Two years before admission to the hospital the Raynaud s phenomenon had extended to involve all the fingers of both hands and to a lesser extent the toes

The major complaint of the patient however, concerned itself with recurrent attacks which followed a definite sequence of events These episodes invariably began with nausea and an intense generalized headache Her hair felt as though it were standing on end and being pulled This was promptly followed by definite precordial throbbing associated with a sensation of marked pulsations in the neck She was dyspneic and during several such episodes actually found herself gasping for breath Her fingers then underwent the characteristic changes previously described These attacks lasted about five minutes and upon their conclusion she was drenched with perspiration and was left utterly fatigued Until three months before admission to the hospital the episodes would occur approximately once a week Since then however they had increased in frequency and severity to the point where they occurred almost every half hour Her blood pressure had been determined two months previously by her physician and found to be 190–200 During the previous four years she had lost approximately 18 pounds in weight

This patient s family history is of considerable interest Her mother and two sisters had had thyroidectomie One of the siblings who had had a thyroidectomy died at the age of twenty-eight with a clinical picture strikingly suggestive of that presented by the patient and according to the hospital records was believed to have been a rare disturbance of the sympathetic system

On physical examination in the hospital the patient was found to be a thin young woman who sweated profusely and appeared to be quite ill The arterioles of the fundi showed slight thinning with increased light reflex There was a well healed thyroidectomy scar at the base of the neck The lungs were clear The heart was not enlarged The second aortic sound was somewhat accentuated, and there was a rough systolic murmur at the base The radial vessels were thickened The blood pressure at the initial examination was 230/180 There was a fine slight tremor of the extended fingers The remain

der of the physical examination was essentially negative No abdominal masses were palpable

While she was in the hospital the attacks recurred at frequent intervals *During the episodes the blood pressure rose from 140/100 to 280/200 millimeters* of mercury

The laboratory studies revealed the *following information The blood* count was normal The urinalysis was essentially negative The blood urea was 25 sugar 175 cholesterol 425 milligrams per cent while the blood sodium was 138 3 milliequivalents per liter On three different occasions the basal metabolic rate was + 69 + 39 and + 27 per cent The electrocardiographic tracing showed a sinus tachycardia with a rate of 115 per minute left ventricular preponderance QRS of high voltage with slight depression of the RT transition in Leads I and II Oscillometric determinations showed diminished peripheral pulsations in the lower part of the legs There was a diminution of skin temperature of the peripheral portions of the body as determined by dermotherm readings The glucose tolerance test showed a fasting blood sugar of 65 milligrams per cent with a rise to 240 milligrams per cent at the end of one hour followed by a fall to 50 milligrams per cent after three hours The patient was given an insulin test consisting of the injection of 10 units of insulin The fasting blood sugar was 102 milligrams per cent and one and one-half hours after injection of the insulin the patient was in profound hypoglycemic shock with a blood sugar of 15 milligrams per cent Epinephrine sensitivity was determined by the subcutaneous injection of 2 minims of adrenalin (1 to 1000) This was followed by an unusually marked increase in the blood pressure level

An attempt was made to demonstrate the presence of a pressor substance in the blood During an attack induced by exercise at which time the systolic blood pressure was over 300 millimeters of mercury 200 cc of blood was removed *from the antecubital vein and its pressor effect compared with the* blood of a control subject by a modification of the Pissemski method of perfusion *of the denervated rabbit s ear This method is sensitive to adrenalin* in a dilution as high as 1 in 100 000 000 With this technic a marked pressor *effect of the patient s plasma could be demonstrated This pressor action* could be reversed by previous perfusion of the rabbit s ear with ergotamine tartrate *in a dilution of 1 to 300 000 These observations suggested the* existence of an active pressor substance in the blood which in view of its *response to ergotamine* was probably adrenalin

A flat plate of the abdomen revealed the presence of a homogeneous shadow *above the position of the left kidney A retrograde pyelogram of this side* showed that the left kidney had been pushed down so that the pelvis was *opposite the body of the third lumbar vertebra and the upper calix* showed definite pressure from above downward A bilateral perirenal insufflation revealed a *large left* adrenal tumor *Upon operation a left adrenal tumor the* size of a grapefruit was removed

*Following the removal of the tumor the patient showed progressive im*provement The periodic attacks had entirely disappeared and the blood pressure remained at 125/85 The basal metabolic rate on two occasions was −1 and −17 per cent The blood urea had fallen to 11 milligrams per cent *the blood sugar* was *75* and the cholesterol was 270 The electrocardiogram remained unchanged Oscillometric readings showed some improvement in *the peripheral circulation* and there was a considerable increase in the peripheral skin temperature The Janney test showed a flat blood sugar curve *Perfusion* experiments now failed to reveal the presence of any pressor substance in the blood

When last seen several years after the operation the patient was perfectly well She had had no attacks since the operation The Raynaud s symptoms *came most infrequently* and only after prolonged exposure to undue cold The systolic blood pressure varied between 125 and 135 millimeters of mercury *and the diastolic* between 85 and 95 *She had* gained considerable weight and pursued a perfectly normal and active life

Comment.—This case is a typical example of the disease. It is worth while noting its long duration and progressive increase both in the frequency and severity of the attacks. The early clinical impression was misleading as so often happens unless we are alert to the possibility of a pheochromocytoma. Following operation there was a complete subsidence of the symptoms.

The following case is abstracted from the report of Thorn and his co-workers[43] and is an example of a pheochromocytoma with persistent hypertension. This patient had been regarded for several years as an instance of malignant hypertension. After the correct diagnosis had been established the removal of the tumor was followed by a striking improvement in the blood pressure.

The patient was a forty year old white woman who entered the Peter Bent Brigham Hospital for the first time in April 1943 with the chief complaint of headache and known hypertension of approximately seven years' duration. In 1934 she had had her first and only pregnancy which terminated in the birth of a normal full term child. During pregnancy the systolic blood pressure readings did not exceed 120 to 130 mm. of Hg. In 1937 during the course of a routine examination a striking elevation in blood pressure (270 mm. Hg systolic and 150 mm. diastolic) was discovered. Subsequent examinations confirmed this finding and the patient was referred to a hospital for more complete study. At that time her chief complaint concerned occasional severe headaches often associated with nausea, rarely with vomiting. The blood pressure was 220 mm. Hg systolic and 120 mm. diastolic. The heart was of normal size without significant murmurs and there was some narrowing in the fundus oculi. No hemorrhages or exudates were noted at this time. Laboratory examinations were not remarkable. Since no etiological factor was disclosed, diagnosis of idiopathic malignant hypertension was made.

In March 1938 her case was again reviewed and no new changes were noted other than a progression of the alterations in the fundi now consisting of marked narrowing of the arteries, wide light streaks, tortuous and engorged veins, marked arteriovenous compression and numerous radial streaks interpreted as old hemorrhages. The blood pressure was found consistently to be elevated ranging from 200 mm. Hg systolic and 150 mm. diastolic to 260 mm. systolic and 160 mm. diastolic. No paroxysms of increased hypertension were noted nor was her blood pressure ever observed to be within normal range. In 1943 before considering the possibility of a sympathectomy for the relief of hypertension, intravenous pyelography was performed. This revealed that the left kidney was abnormally low in position with a soft tissue mass above it. A tentative diagnosis of adrenal tumor was made. Inquiry at this time revealed no history of paroxysmal attacks of palpitation, sweating, tremor, dizziness or weakness.

Physical examination revealed a well nourished white woman in no acute distress. The blood pressure was 270 millimeters Hg systolic and 160 mm. diastolic in both arms. The arteries of the fundus oculi were very narrow with a sharp light streak, the veins were distended and tortuous, there was striking arteriovenous compression and small white lines radiating from the discs with no evidence of recent hemorrhage, exudates or papilledema. The heart was slightly larger than normal. The first heart sound at the apex was accentuated, the aortic second sound was exceedingly loud and ringing, there were no murmurs and the heart rate was regular. No masses could be felt in the abdomen. The blood pressure in both legs was 250 mm. Hg systolic and 150 mm. diastolic to 270 mm. systolic and 160 mm. diastolic.

Laboratory examination. Urinalysis revealed a specific gravity which varied from 1.010 to 1.015, a slight trace of albumin with occasional red blood cells, white blood cells, hyaline and granular casts. Blood chemical studies

revealed a blood urea nitrogen of 14 mgm non protein nitrogen 23 mgm serum protein of 7 3 grams serum albumin 3 9 gm serum globulin 3 4 gm blood sugar 81 mgm , and blood cholesterol of 235 mgm per 100 cc Serum chloride was 100 meq per liter Phenolsulphonphthalein test revealed 25 per cent of the dye excreted in fifteen minutes and a total of 50 per cent in two hours An *oral glucose tolerance curve revealed a fasting blood sugar level of 130 mg* per 100 cc one-half hour after ingestion of 100 gm of glucose the blood sugar was 100 mg at one hour 68 mg at two hours 77 mg and at three hours 85 mg Roentgenogram of the heart showed it to be transverse in position prominent to the left with an elongated tortuous aorta An electrocardiogram revealed an abnormal form of ventricular complex with T_1 and T_2 diphasic and T_3 inverted A sodium amytal blood pressure depression test with the use of 0 4 gm of the drug in a single dose was followed by a lowering of blood pressure from a level of 240 mm Hg systolic and 140 mm diastolic to 180 mm systolic and 110 mm diastolic An intravenous pyelogram revealed a large soft tissue mass visible above the left kidney

Following removal of a large left pheochromocytoma the patient eventually made an uneventful recovery At the time of her discharge from the hospital the blood pressure averaged 160 millimeters of mercury systolic and 100 millimeters diastolic The retinal examination revealed a progressive disappearance of the fundal changes noted on admission Nine months after the operation the patient apparently felt well the headaches had disappeared and the resting blood pressure was 140 systolic and 88 diastolic

Neither of the patients cited above developed glycosuria or hyperglycemia *The degree of disturbance in carbohydrate metabolism which may* be manifested by these patients however is well exemplified in the case recently reported by Duncan Semans and Howard [63] Their patient was a sixty five year old Negro who was originally admitted to the Johns Hopkins Hospital for diabetic regulation following an acute respiratory infection His illness had started three years prior to admission to the hospital and was characterized by polyuria frequent throbbing headaches and sweats While in the hospital his fasting blood sugar varied between 290 and 336 milligrams per cent and the CO combining power was 63 volumes per cent The urine showed considerable sugar and traces of acetone The blood pressure fluctuated widely between 115 millimeters of mercury systolic and 70 millimeters diastolic and 250 millimeters of mercury systolic and 113 millimeters diastolic The basal metabolic rate varied between +25 and +48 per cent

On a fairly liberal diet of approximately 2300 calories daily consisting of C 250 F 120 and P 80 he required 15 units of protamine zinc insulin and 30 units of regular insulin On this regimen he still manifested some glycosuria while his fasting blood sugar level was frequently elevated

Within ten days after the removal of a pheochromocytoma involving the right adrenal the glycosuria and fasting hyperglycemia had disappeared completely although insulin had been discontinued and the daily carbohydrate content of his diet increased to 300 grams The blood pressure had fallen to approximately 120 80 and was maintained at this level while the basal *metabolic rate was now −4 per cent This patient was followed for a* period of five months during which time he evidenced neither hypertension nor signs of diabetes

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Section III The Gonads

Chapter 15

THE TESTIS

EMBRYOLOGY OF THE GENITAL SYSTEM. ANATOMY OF THE MALE GENITALIA. GROSS ANATOMY AND HISTOLOGY OF THE TESTIS. SPERMATOGENESIS. THE MALE ACCESSORY GENITALIA. THE EMBRYONIC GONAD AND ABNORMAL SEXUAL DEVELOPMENT

By ARTHUR R. SOHVAL, M.D.

Introduction.—By virtue of its exterior location and ready availability for inspection and manipulation, the testis was easily the first endocrine gland to engage the interest of ancient man. In fact, the earliest recorded observations of endocrinologic significance derive from castration procedures performed on male animals and man. The effects on sexual drive, hair growth and voice were described by Aristotle.[1] Knowledge of the effects of castration led to the staffing of Oriental harems with eunuchs. Because of their high pitched voice quality, *castrati* were employed in papal choirs as late as the 18th century. Adoption of castration by a secret and outlawed religious sect in Rumania and Russia known as the Skoptsi provided material for the first clinical studies on male hypogonadism.[2]

During the past few decades there has been a vast accumulation of experimental and clinical data which enables us to formulate well authenticated concepts concerning the function of the testis and its role in the complex interrelationships of the endocrine glands. Although many gaps in our knowledge exist, these are being reduced gradually by the rapidly multiplying efforts of interested investigators.

The testis is concerned primarily with reproduction of the species. It accomplishes this by the formation of spermatozoa and the elaboration of an internal secretion. The latter has a profound effect on the accessory male genitalia in addition to being essential for sperm production. For this reason, the testis cannot be studied and described as an isolated anatomic and functional entity but rather must be considered in conjunction with the entire genital system.

EMBRYOLOGY OF THE GENITAL SYSTEM

A fuller comprehension of the anatomy and pathophysiology of the testis is to be obtained from a knowledge of its embryologic development. An understanding of the complicated embryology of the reproductive system is also essential for the elucidation of the poorly understood sexual and hormonal interrelationships between the male and female. Aberrations of

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first as a thickening of the peritoneal epithelium on the medial aspect of the urogenital ridge. The superficial layer of cells, now called the *germinal epithelium*, continues to proliferate and produces the genital ridge which runs parallel to the mesonephric ridge. Further proliferation of the germinal epithelial cells occurs inward to form an *internal epithelial mass* which becomes the indifferent or undifferentiated sex gland.[5] By the seventh week (17 mm.) the specific characteristics of testis or ovary can be identified. Before sexual differentiation occurs, however, *primordial germ cells* can be recognized as large, distinctive cells lying both in the proliferating layer of germinal epithelium and within the internal epithelial mass. Although it would seem to follow that these primordial germ cells must originate from the superficial proliferating layer, there is considerable controversial opinion regarding their origin.[6] Similar cells have been observed at a considerable distance from the internal epithelial mass in the yolk sac entoderm, gut entoderm and dorsal mesentery, whence they are said to migrate into the epithelium of the genital ridge.[7] In addition to the disputed origin of the primordial germ cells, there are conflicting views as to whether or not they constitute the sole source of future germ cells.[8] Some observers hold that new germ cells are derived from the germinal epithelium as the older cells degenerate. The indifferent sex gland, consisting of a surface layer of germinal epithelium enclosing an internal epithelial mass which has proliferated from it, undergoes further development prior to differentiation. Within the substance of the gonad branching and anastomosing strands of cells appear. These are known as *primary sex cords* and, although in most vertebrates they arise directly from the germinal epithelium, Arey[9] is of the opinion that in man they organize themselves from the internal cell mass itself. They soon become separated from the overlying layer of germinal epithelium by a layer of connective tissue, the *tunica albuginea*. Development beyond this point proceeds along the lines of sexual differentiation into the male or female gonad.

Testis Differentiation.—The indifferent gonad destined to become a testis shows recognizable changes somewhat earlier than the gonad which is to become the female sex gland. The primary sex cords, now known as the *testis cords*, arrange themselves radially, converging toward the region of attachment of the gonadial mesentery, now termed the *mesorchium*. Here the epithelial mass has formed the *rete testis*, a network of cords which soon unites with the testis cord, the two elements constituting the forerunners of the *seminiferous tubules*. Although these structures are called tubules, they do not develop lumens until puberty.[10] Whereas the rete tubules persist as an anastomosing network, the adjacent portions of the seminiferous tubules remain straight as the *tubuli recti* and the peripheral portions become the elongated, coiled and twisted *tubuli contorti*. As the rete cords establish connection with the testis cords, they simultaneously unite with persistent mesonephric tubules, the latter becoming the *ductuli efferentes* of the epididymis.

The large, pale primordial germ cells originally present in the primitive internal cell mass are not found in the early testis cords. However, as the latter develop their characteristic radial arrangement and communication with the rete cords, large pale cells again appear among its indifferent

sexual development hermaphroditism, pseudohermaphroditism and the *endocrine aspects of genital neoplastic disease are best studied in the light* of the common fetal origin and subsequent sexual differentiation of the male and female primordial gonads.* For this reason the embryologic development of the male reproductive system will be treated in conjunction with that of the female.

The reproductive system in man, as in vertebrates in general, has a common origin with the urinary system. Both are known in early embryonic life as the *urogenital system*. As one traces the growth and development of the embryo, it is apparent that anlagen for both sexes always exist in the earliest stages and that sexual differentiation normally proceeds in an orderly fashion with preservation of homologous fetal structures and *degeneration of most of the heterologous counterparts. Certain of the* latter are retained in the adult as vestigial remnants.

It will be recalled that the urinary system in man develops successively three different types of excretory organs, each caudad to the other. In so doing it classically recapitulates the phylogenetic principle.

The first excretory organ is the *pronephros*, functional today only in the Amphioxus and certain lampreys. It is functionless in man and appears toward the cephalic extremity of the embryo. It degenerates at the end of four weeks (5 mm.), leaving only its duct for future use. Its function is replaced by the *mesonephros* (Wolffian body) which is a larger structure situated further caudad.

In the *mesonephros only tubules (about thirty in number)*[4] are formed. It utilizes the pronephric duct as its own excretory duct which is now known as the *mesonephric (Wolffian) duct*. The mesonephros plays a vital role in the development of the male genital tract and is fully developed at seven weeks (17 mm.) which coincides with the initial appearance of sex differentiation in the gonads. As parts of the mesonephric tubules and duct are incorporated into the developing genital system (principally the male) there is a progressive degeneration of the more cranial tubules and a formation of new tubules caudally. This process has the effect of shifting the organ toward the caudal end of the embryo. By the fifth month degeneration of the non merged mesonephric tubules is complete.

The excretory function of the fetal urinary system is now taken over by the third or permanent kidney, the *metanephros*. All three kidney types are aggregates of uriniferous tubules having a common origin from the mesoderm of the nephrotome. At the height of its development the paired mesonephros extends longitudinally on either side of the dorsal mesentery for almost the entire length of the celomic cavity into which it bulges. This longitudinal ridge is known as the *urogenital ridge* and early subdivides longitudinally into a lateral *mesonephric ridge* and a median *genital ridge*.

The genital system appears slightly later than the urinary system, becoming evident during the fifth and sixth weeks (5 to 12 mm.). It appears

* The adrenal cortex also plays a rôle in the elaboration of male and female sex hormones. Under certain circumstances the magnitude of this rôle may assume sufficient proportions to alter seriously the secondary sex characteristics of the individual. The embryonic proximity of the adrenal gland to the undifferentiated sex gland is all important in this connection and is considered in another chapter.

nective tissue cell Although the origin of these cells has not been definitely established the weight of evidence points to the ovarian mesenchyme itself [15 16 17] In Meyer's opinion[18] superfluous masses or rests of indifferent epithelial cells may persist as a nidus for the formation of granulosa cell tumors of the ovary in later life A similar mechanism would account for the theca cell tumor of the ovary Furthermore a common origin of the progenitors of these two types of cells would explain the functional and histologic kinship of these two feminizing neoplasms

The supportive connective tissue framework of the ovary lacks the structural regularity of its counterpart in the testis but in general resembles it closely It appears early in the rete ovarii as an ingrowth from the mesovarium accompanied by a developing vasculature Extensions into the substance of the ovary form the interlacing stroma which fuses at the periphery of the ovary as the *tunica albuginea* coat This layer of loose connective tissue not as well developed as in the testis lies just beneath the encapsulating layer of germinal epithelium

Development and Differentiation of the Genital Ducts —Concurrently with the development of the indifferent sex gland a male (Wolffian) and female (Mullerian) sex duct becomes available in each embryo When the sex gland differentiates into a testis the mesonephric duct and some of its tubules are appropriated to become the male genital duct A group of cephalically placed mesonephric tubules become the *ductuli efferentes* and communicate with the rete testis The proximal portion of the mesonephric duct becomes the highly coiled duct of the *epididymis* which receives the efferent ducts The remainder of the mesonephric duct is transformed into the *ductus deferens* which terminates in the urethra Immediately proximal to this junction the *seminal vesicle* appears as an outpouching of the duct The prostate gland and Cowper's gland differentiate from the urethra A few functionless cephalic mesonephric tubules persist as the *appendix epididymis* while the caudal group of tubules remain as the blindly ending *paradidymis* and *aberrant ductules* The entire Mullerian duct degenerates except for its extreme proximal extremity which remains as the *appendix testis* and its terminal portion where it is fused with its mate from the opposite side to form the *prostatic utricle* (*vagina masculina*)

Differentiation of the sexless gonad into an ovary is accompanied by retention of the Mullerian duct system for purposes of ovum transport The Mullerian duct appears somewhat later than and lateral to the mesonephric duct both being situated in the mesonephros As the duct extends caudad it turns medially to fuse with its mate from the opposite side forming *Muller's tubercle* The united portions will form the uterus and upper vagina while the upper segment will serve as the fallopian tube Pari passu with Mullerian duct development the mesonephric system regresses Some of the cranial tubules persist without function as the *epoophoron* while others remain as the *vesicular appendices* The caudal group of tubules may be recognized in childhood as the *paroophoron* which usually disappears before puberty While the major portion of the mesonephric duct degenerates a small vestigial remnant is found in about one fourth of females as the *duct of the epoophoron* or *Gartner's duct* A detailed tabulation of the ultimate derivatives of the indifferent urogenital system is provided in Table 22

cellular elements These are identified as *spermatogonia* and it is not definitely known whether they are derived from the primordial germ cells or from the indifferent elements The spermatogonia and the indifferent elements persist as the only cellular constituents of the testis tubules until puberty at which time a lumen appears and spermatogenesis begins. Simultaneously, *sustentacular cells* (of Sertoli) are developed from the indifferent cells to serve as supporting structures and nourishing elements for the spermatids

The cellular cords of the testis are maintained in their characteristic architectural pattern by a contiguous connective tissue framework Directly underlying the germinal epithelium is the tunica albuginea which joins the connective tissue partitions between the lobule These partitions called *septula* in turn converge toward and join the connective tissue embedding the rete testis the *mediastinum testis* Within the stroma of the connective tissue and interspersed between the seminiferous tubules are the large, polyhedral pale *interstitial* cells (of Leydig) They are less numerous and less developed in the newborn but a second generation appears at or after puberty [11] It is generally conceded that the endocrine secretion of the testis derives from these cells

Ovary Differentiation — As the indifferent sex gland veers in the female direction its radially disposed primary sex cords converge toward the hilum as in the testis However they do not form the anastomosing columns distinctive of testis cords nor do they establish communication with the mesonephric tubules These irregular *medullary columns* arrange themselves into a relatively dense *primary cortex* and a looser internal *primary medulla containing early primordial ova* At the same time a compact mass of epithelial cells extends into the *mesovarium* from the medulla with the formation there of the *rete ovarii* (homologue of rete testis) The mesovarium the counterpart of the mesorchium is the original mesentery of the mesonephros

According to Novak [1] the primary sex cords soon disappear although vestigial rests may persist in the hilum in the region of the rete ovarii He is of the opinion that from certain male-directed remnants the masculinizing tumor of the ovary known as arrhenoblastoma may arise in later life

Disappearance of the primary sex cords (medullary columns) is accompanied and followed by rapid enlargement of the ovary This is due to the formation of secondary sex cords (of Pfluger) resulting in a *secondary cortex* The actively proliferating germinal epithelium is regarded as the source of these sex cord ingrowths [13] although this origin has been questioned [14] The majority of the cells at the periphery of the ovary becomes transformed into young ova while the earlier ova in the primary cortex and medulla degenerate In this manner the permanent medulla with its vascular fibrous stroma is formed

The young ova richly *dispersed in the secondary cortex persist and* become surrounded by indifferent epithelial cells to produce the *primary follicles* Several hundred thousand exist at the time of birth

The encapsulating epithelial cells of the primordial follicles later become the *granulosa cells* of maturing follicles Another cellular component which appears later in this connection in the *theca cell* a specialized type of con-

nective tissue cell Although the origin of these cells has not been definitely established the weight of evidence points to the ovarian mesenchyme itself[15,16,17] In Meyer's opinion[18] superfluous masses or rests of indifferent epithelial cells may persist as a nidus for the formation of granulosa cell tumors of the ovary in later life A similar mechanism would account for the theca cell tumor of the ovary Furthermore a common origin of the progenitors of these two types of cells would explain the functional and histologic kinship of these two feminizing neoplasms

The supportive connective tissue framework of the ovary lacks the structural regularity of its counterpart in the testis but in general resembles it closely It appears early in the rete ovarii as an ingrowth from the mesovarium accompanied by a developing vasculature Extensions into the substance of the ovary form the interlacing stroma which fuses at the periphery of the ovary as the *tunica albuginea* coat This layer of loose connective tissue not as well developed as in the testis lies just beneath the encapsulating layer of germinal epithelium

Development and Differentiation of the Genital Ducts —Concurrently with the development of the indifferent sex gland a male (Wolffian) and female (Mullerian) sex duct becomes available in each embryo When the sex gland differentiates into a testis the mesonephric duct and some of its tubules are appropriated to become the male genital duct A group of cephalically placed mesonephric tubules become the *ductuli efferentes* and communicate with the rete testis The proximal portion of the mesonephric duct becomes the highly coiled duct of the *epididymis* which receives the efferent ducts The remainder of the mesonephric duct is transformed into the *ductus deferens* which terminates in the urethra Immediately proximal to this junction the *seminal vesicle* appears as an outpouching of the duct The prostate gland and Cowper's gland differentiate from the urethra A few functionless cephalic mesonephric tubules persist as the *appendix epididymis* while the caudal group of tubules remain as the blindly ending *paradidymis* and *aberrant ductules* The entire Mullerian duct degenerates except for its extreme proximal extremity which remains as the *appendix testis* and its terminal portion where it is fused with its mate from the opposite side to form the *prostatic utricle* (*vagina masculina*)

Differentiation of the sexless gonad into an ovary is accompanied by retention of the Mullerian duct system for purposes of ovum transport The Mullerian duct appears somewhat later than and lateral to the mesonephric duct both being situated in the mesonephros As the duct extends caudad it turns medially to fuse with its mate from the opposite side forming *Muller's tubercle* *The united portions will form the uterus* and upper vagina while the upper segment will serve as the fallopian tube Pari passu with Mullerian duct development the mesonephric system regresses Some of the cranial tubules persist without function as the *epoophoron* while others remain as the *vesicular appendices* The caudal group of tubules may be recognized in childhood as the *paroophoron* which usually disappears before puberty While the major portion of the mesonephric duct degenerates a small vestigial remnant is found in about one fourth of females as the *duct of the epoophoron* or *Gartner's duct* A detailed tabulation of the ultimate derivatives of the indifferent urogenital system is provided in Table 22

cellular elements These are identified as *spermatogonia* and it is not definitely known whether they are derived from the primordial germ cells or from the indifferent elements The spermatogonia and the indifferent elements persist as the only cellular constituents of the testis tubules until puberty at which time a lumen appears and spermatogenesis begins Simultaneously, *sustentacular cells* (of Sertoli) are developed from the indifferent cells to serve as supporting structures and nourishing elements for the spermatids

The cellular cords of the testis are maintained in their characteristic architectural pattern by a contiguous connective tissue framework Directly underlying the germinal epithelium is the tunica albuginea which joins the connective tissue partitions between the lobules These partitions called *septula* in turn converge toward and join the connective tissue embedding the rete testis the *mediastinum testis* Within the stroma of the connective tissue and interspersed between the seminiferous tubules are the large, polyhedral pale *interstitial* cells (of Leydig) They are less numerous and less developed in the newborn but a second generation appears at or after puberty [11] It is generally conceded that the endocrine secretion of the testis derives from these cells

Ovary Differentiation —As the indifferent sex gland veers in the female direction its radially disposed primary sex cords converge toward the hilum as in the testis However they do not form the anastomosing columns distinctive of testis cords nor do they establish communication with the mesonephric tubules These irregular *medullary columns* arrange themselves into a relatively dense *primary cortex* and a looser internal *primary medulla* containing early primordial ova At the same time a compact mass of epithelial cells extends into the *mesovarium* from the medulla with the formation there of the *rete ovarii* (homologue of rete testis) The mesovarium the counterpart of the mesorchium is the original mesentery of the mesonephros

According to Novak [1] the primary sex cords soon disappear although vestigial rests may persist in the hilum in the region of the rete ovarii He is of the opinion that from certain male-directed remnants the masculinizing tumor of the ovary known as arrhenoblastoma may arise in later life

Disappearance of the primary sex cords (medullary columns) is accompanied and followed by rapid enlargement of the ovary This is due to the formation of secondary sex cords (of Pfluger) resulting in a *secondary cortex* The actively proliferating germinal epithelium is regarded as the source of these sex cord ingrowths[13] although this origin has been questioned [14] The majority of these cells at the periphery of the ovary becomes transformed into young ova while the earlier ova in the primary cortex and medulla degenerate In this manner the permanent medulla with its vascular fibrous stroma is formed

The young ova richly dispersed in the secondary cortex persist and become surrounded by indifferent epithelial cells to produce the *primary follicles* Several hundred thousand exist at the time of birth

The encapsulating epithelial cells of the primordial follicles later become the *granulosa cells* of maturing follicles Another cellular component which appears later in this connection in the *theca cell* a specialized type of con

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TABLE 22.—ULTIMATE DERIVATIVES OF THE INDIFFERENT UROGENITAL SYSTEM (AREY. DEVELOPMENTAL ANATOMY. W. B. SAUNDERS CO.)

Male	*Indifferent Stage*	*Female*
Testis	Gonad	Ovary
(1) (2) Seminiferous tubules (3) Rete testis		(1) Cortex (2) Medulla (primary) (3) *Rete ovarii*
(1) *Mesorchium* (2) (3) *Ligamentum testis* (4) *Gubernaculum testis* (in part) (5) *Gubernaculum testis* (as a whole) (6)	Genital ligaments	(1) Mesovarium (2) Suspensory ligament of ovary (3) Proper ovarian ligament (4) Round ligament of uterus (5) (6) Broad ligament of uterus
Efferent ductules and *appendix epididymidis* *Paradidymis* and *aberrant ductules*	Mesonephric tubules Cranial group Caudal group	*Epoöphoron* and *vesicular appendices* *Paroöphoron*
(1) Ductus epididymidis (2) Ductus deferens (3) Seminal vesicle (4) Ejaculatory duct	Mesonephric (Wolffian) duct	*Gartner's duct of the epoöphoron*
(1) *Appendix testis* (2) (3)	Müllerian duct	(1) Uterine tube (2) Uterus (3) Vagina (upper part?)
Seminal colliculus	Müller's tubercle	Hymen (site of)
(1) Bladder (except trigone?) (2) Upper prostatic urethra	Vesico-urethral primordium	(1) Bladder (except trigone?) (2) Urethra
(1) Lower prostatic urethra (a) *Prostatic utricle* (or *vagina masculina*) (b) Prostate gland (2) Membranous urethra (3) Cavernous urethra Bulbo-urethral glands	Urogenital sinus Pelvic portion Phallic portion	(1) Vestibule (nearer the vagina) (a) Vagina (lower part at least) (b) *Para-urethral ducts* (2) Vestibule (middle part) (3) Vestibule (between labia minora) Vestibular glands (of Bartholin)
(1) Penis (a) Glans penis (b) Urethral surface of penis (c) Corpora cavernosa penis (d) Corpus cavernosum urethrae (2) Scrotum (3) Scrotal raphé (4)	Phallus Glans Lips of urethral groove Shaft Labio-scrotal swellings Median swelling	(1) Clitoris (a) Glans clitoridis (b) Labia minora (c) Corpora cavernosa clitoridis (d) Vestibular bulbs (2) Labia majora (3) Posterior commissure (4) Mons pubis

ANATOMY OF THE MALE GENITALIA

The Gross Anatomy of the Testis —The testes are contained in a pouch like scrotum which is divided into two compartments by a septum Each testis is lodged in its own chamber It is ovoid and slightly flattened from side to side with average measurements of 4 to 5 cm in length and 2 5 to 3 cm in width The average weight of the adult testis is about 25 grams with a range of 10 to 45 grams The testis is obliquely placed so that the medial surface also looks slightly anteriorly and inferiorly As a rule the left testis is at a somewhat lower level than the right The medial and lateral surfaces and the anterior border are free of attachments while the posterior border is attached to the spermatic cord and epididymis The head and tail of the epididymis are attached to the superior and inferior extremities of the testis respectively

The blood vessels and lymphatics of the spermatic cord and the efferent ductules of the epididymis enter the testis on its posterior border toward its upper part This region of the testis is known as the *mediastinum* (*corpus Highmori*) and is composed of connective tissue In it is embedded the *rete testis* a meshwork of tubules which drain the seminiferous tubules and also communicate with the ductules of the epididymis Radiating peripherally from the mediastinum are thin connective tissue partitions the *septules* which subdivide the interior of the testis into numerous pyramidal lobules The testis contains about 250 lobules each enclosing several highly convoluted thread like seminiferous tubules Each tubule has a length of 30 to 70 cm and an average diameter of about 250 to 300 microns Communication between tubules of adjacent lobules occurs through perforate interlobular septa As the convoluted tubules converge toward the hilum their terminal portions straighten out to form the *tubuli recti* which enter the anastomosing network of the rete testis in the mediastinum

The septa extend to the periphery of the gland where they join the dense connective tissue capsule known as the *tunica albuginea* Externally the visceral layer of the tunica vaginalis is closely applied to the surface of the testis except where the latter is attached to the spermatic cord and epididymis A fold of this layer extends in between the testis and the epididymis forming the *sinus epididymis*

In contact with but not adherent to the visceral layer is the parietal layer of the tunica vaginalis which lines the scrotal sac Together these two layers form a closed serous sac which represents the original vaginal process of peritoneum The antenatal extension of the latter through the inguinal canal into the scrotum paves the way for the descent of the testis from its intraabdominal position

The *blood supply* of the testis is derived principally from the *internal spermatic artery* a branch of the aorta To a lesser extent blood is furnished by the *deferential* and *cremasteric* arteries branches of the *inferior vesical* (sometimes of the *superior vesical*) and *deep epigastric* arteries respectively All three arteries anastomose so that injury to one artery does not result in atrophy of the testis [19] The venous return from the testis empties into the *pampiniform plexus* and thence enters the *spermatic veins* While the right



Fig 349
Squamous Cell C c oma (Ep thel om)—An e ly tumour with the downgro ths of epithel l processes st ll s perficial and w ll-defined b t w th typ cal central cornificat on (cell est) in th m
Hæmalum and Eos n × 45

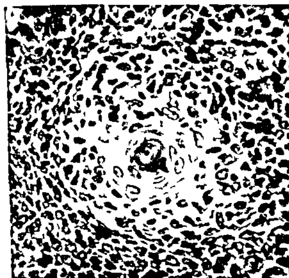


Fig 350
Squamous C ll Car inoma (Epithel oma)—Th s tumour arose from a nævus sebaceus A typ cal cell est fr m ne of the ep thelial processes shown
Hæmalum and Eosi 400

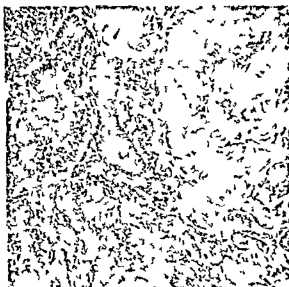


Fig 351

Squan ou Cell Ca oma (Epithel m)—In th s example there is nvasion of the derm s by ab ndant tum our masses but central c rnificat on is mperf ct in them Th re is a heavy infiltrat n of th stroma by chron c nflammatory cells

Hæmalum and E in × 70

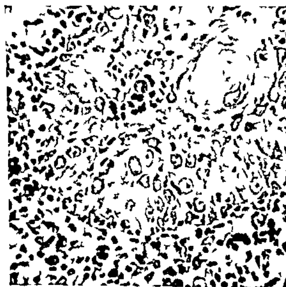


Fig. 35?

Squamous C ll C cinoma (Epithel oma) The same as F g 351 A port of a tumour p ocess show g in t s hst nce small cell nest surrou nded by squamous ep thel al cells I th adj ce t stroma ar ma y chr n c infl mmat ry c ll —lymphocytes pla ma cel and larger h st ocytes

Hæmal m and Eosin 400

/

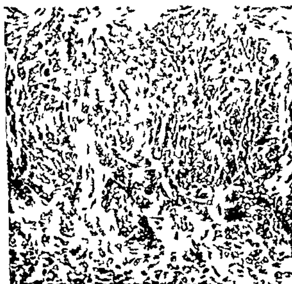


Fig 353

Sq iamou Cell Ca cinoma (Ep thel oma)—*An plast c type* O ly a port n of a ep th l l proces is shown but it is typ c l of the others Th r i no d fferent at w th formati n of cell nests the tum r cell being so clos ly p cked that the r squamou charact rist cs e d fficult to d term ne M y cells ha m totic figures in them wh h sta n d rker a d ar m re comp ct than the ord nary n cle

Hæmalum and Eo in × 175



FIG. 354

Squamous Cell Carcinoma (Epithelioma).—This specimen was taken from the hip of a man aged 84 who had a tumour there for three years. This is a portion of more recent actively growing area. There is excessive surface cornification and thick growths of tumour masses most of which have extensive central degeneration with actual cornification in a few places.

Hæmalum and Eosin × 20



FIG. 355

Squamous Cell Carcinoma (Epithelioma).—This shows in more detail the swelling and degeneration of the cells in the centre of the tumour process with an imperfect "cell nest" at the side of one process.

Hæmalum and Eosin × 80



FIG 356

Squam Cell Carcinoma (Ep thelioma)—F om the same pat ent the specimen sh wn n Fig 354 This part of the tum ur has been prese t for three yea s It is rel tively ben gn ep thelioma showing e tensive d generation in the centr l parts of the broad processes

Hæmalum and E n × 20



FIG 357

Squamou -C ll Ca noma (Ep thel oma)—To show i mo e detail a port n f the t m r hown n Fig 356 In the ce tr is large ar a f d br f rmed by broken down tumo r cell out d of th is a wide z ne f poo ly sta ng cl r cells undergoing degene t n At the periphery ar the ord nary squamou cells f di g i to the zone of degeneration o the one sid nd harply defined on the outer s de by the fibrous stroma \ port n of the d rm s is i cluded bey d th s.

Hæmalum and Eos n × 80



FIG 358

Cal ified Squamou C ll Ca cinoma (Ep thel oma)—This was a ery sl w growing tum r with exten i e con fic t n Th ep thelial proces s are shown with a ma s of corn fied d bris in wh ch r d k bl e st ning deposits of calcium
Hæmal m a d Eosin × 75



FIG 359

Squamous Cell Ca cinoma Pa affn Carci oma—The ep d rmis is hyperkerat t c In the s bj ce t dermis there is a w despre d infiltrat on by th epith li l process s f the tum r which show central corn ficati in the superfici l r but l ttl different at on deeper—at the gr wi g marg n

Hæmalum and Eos n × 12½

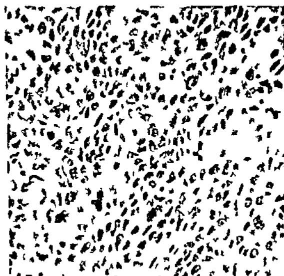


FIG 360

Squamous C ll Carcinoma Pa affin Carcinoma—Deep part f the tumour shown in F g 359 The epith-l l p ocesses e nume us ll-d fned, d composed of polygonal c ll w th no tt mpt at d fferentiat on i e an anapl st type of squamous-cell cinoma (ep thel om)

Hæmalum and Eosin 300



Fig 361

X ray Carc oma—Ther is much rfa e ker tinisat n a d typical down growths of epith l l processes many of which h e the usual centr l corn ficat n It is a squ mou cell c rci oma (pithel ma)

Hæmalum and Eosin × 20



Fig. 3o?

Squamous C ll C noma superimposed upon Lupus V lga —No trace r ia ns in the ection of the original lupus, but the d rm is exten ely filtrated by an ep th l oma which has u de gone cessive c rn ficat on

Hæmalum a d Eosin 2>



FIG 365

Cut neou H rn—A th k hyperpl stic lay r of ep d rm s f ms the ba e fr m wh ch projects a p ll r of h rd ker t nised m t al Th horn fissu ed n the sect g wing to t hard d to gh char cter Amongest th h rny m tter e blu st ed calcareou depos t The unaff cted ep d rm of n rmal th ckn is een a the edges f th hyperplast c ba

Hæm lum nd E n 7



Fig 366

I t a ep de m l Ca noma—Paget s D sease—The ep derm l p thel m s ded and largely repl ced by th Paget cells—large pale ta ing cl ar cell I tn surr u d g derm s th r great nfl mmatory re ct n i the f rm of gr ul t n t ss e hea lv i filtrated with i fl mmat ry cells *Hæmalum and E s n* 65

PSORIASIFORM CARCINOMA SHOWING DIFFERENT TYPES OF MALIGNANCY IN VARIOUS AREAS OF THE SAME LESION



FIG. 367

Pso form carc oma—He e are seen downgrowths f the ep d rmis w th the f rmat of processe and masses of p th l al cell h ı g the arr ngem t a d haracters of an ep d rmoid carc n m of basal c ll type *Hæm lum and Eos n* × 100

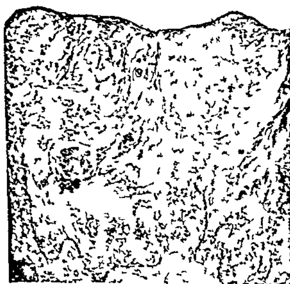


FIG. 368

Pso s f rm carcinoma—I th a there mu h hyperplas a f the ep derm s, the cells of which r la ge nd cl Th deeper layers e commenc g t penetr t ı to the sub ı cent derm and show an rly tt mpt t ce t l corn f t on ı e he e the mal gnancy is f the sq amou p thelioma t pe *Hæmalum and Eosin* 70

adenohypophysis is capable of hyperfunctioning at least in regard to the production of gonadotropin for a great number of years

Postpuberal castration results in a much less striking clinical picture Since mature and normal skeletal and genital proportions had been attained prior to castration the effects on these structures are absent or minimal Consequently, the eunuchoid habitus is absent The bony frame is not altered grossly and the genitalia remain large except for the scrotum, the size of which apparently depends in part on that of the enclosed organs [6] Libido and sexual potency may be retained in a limited degree especially if the individual had previously established a mature psychosexual pattern Although penile erections are usually limited in frequency and completeness satisfactory coitus is occasionally possible

The mature voice of the postpuberal eunuch is maintained to a large extent although special tests may reveal a slight rise in pitch

Hair growth is not as sharply curtailed as it is in the prepuberal castrate Shaving may be required once or twice a week The hair of the body extremities pubis and axillae becomes somewhat sparser and finer and the eyebrows less bushy

Vasomotor symptoms such as hot flushes sweating and dizziness are frequently present in the postpuberal castrate especially in the immediate postoperative period Since these phenomena do not appear in the individual castrated prior to puberty it is highly probable that they are related to the sudden withdrawal of male sex hormone from an organism previously adjusted to it The mechanism is similar to that involved in the production of menopausal symptoms in the female and the resulting symptoms are referred to as the male climacteric

Except for the specific differences just indicated the changes induced by castration after puberty are identical with those occurring in the prepuberal eunuch

The *therapy* of eunuchism is necessarily substitutional and involves the use of androgenic compounds It is imperative that treatment of the prepuberal castrate be instituted at the age of eleven or twelve years if irreversible eunuchoid skeletal changes are to be avoided However even if the patient has already developed a eunuchoid habitus he will be strikingly benefited by treatment Furthermore even castrates of many years duration undergo marked improvement as a result of androgen therapy

Testosterone propionate is the most effective androgen and 20 mg in oil injected intramuscularly 6 or 7 times a week has been found to be an adequate replacement dose in a large group of castrates [77] For practical purposes an injection of 50 mg 3 times a week is more satisfactory although in some instances double this dose may be necessary [83]

A more convenient although more expensive method of treatment is the oral administration of methyltestosterone Quantities about 4 to 6 times greater than those of testosterone propionate given intramuscularly produce equivalent androgenic effects The oral effectiveness of this compound is probably due to the fact that it is absorbed from the intestinal tract directly into the lacteals instead of the blood Its passage into the thoracic duct enables it to enter the systemic circulation directly thereby by passing the liver where it would be subjected to conjugation and in

activation However, in addition to its being 2 to 3 times as expensive as testosterone propionate milligram for milligram, methyltestosterone at times causes nausea, vomiting, headache, vertigo and a burning sensation in the mouth Furthermore Werner[49] has called attention to the occasional occurrence of mild icterus during the use of this compound This is infrequent and while readministration of the drug resulted in a recurrence of jaundice in one patient it failed to do so in another It must be emphasized that these untoward effects are mild and uncommon and should not deter the physician from using the compound when it is indicated Full replacement therapy for the eunuch requires a daily dosage of 150 mg (two 25 mg tablets 3 times a day)

Since castrated patients require replacement therapy throughout life it is often advisable to implant testosterone pellets subcutaneously This is usually done after a full therapeutic effect has been achieved by injections and the patient is ready for maintenance therapy Six to 8 pellets of testosterone propionate weighing 75 mg each provide a steady source of stimulation which suffices for three to six months depending on the rate of absorption

Tablets of free testosterone or its propionate ester are also employed for sublingual or buccal absorption Approximately the same dosage as that used parenterally is said to have equivalent effects The purpose of this mode of administration is to enable the androgen to enter the systemic circulation directly and thus avoid gastro-intestinal and hepatic inactivation However it requires about thirty to sixty minutes for the tablet to dissolve during which time the patient must avoid eating drinking or swallowing The occurrence of salivation in response to the presence of the tablet makes it difficult to avoid a loss by swallowing Furthermore insufficient data have been accumulated to date to verify the efficacy of this type of therapy

Crystals of free testosterone suspended in water are also of value when injected intramuscularly The poor solubility of the crystals is utilized to provide a slow gradual absorption from the injected depot after the water is absorbed This method has the advantage of requiring fewer injections (about once a week) but insufficient information is available as yet concerning its effectiveness as compared with the injection of the propionate in oil

Testosterone is absorbed percutaneously from an ointment but is least effective when employed in this manner Self administration by the patient renders this method subject to his whims and is therefore unreliable This form of treatment is not recommended

The administration of adequate androgen therapy to the prepuberal castrate before or during the age of puberty allows the normal development of the skeleton genitalia hair and musculature The pitch of the voice will also become lowered to that of the mature adult If treatment is delayed until after the completion of puberty the skeletal disproportion persists but the accessory genitalia and the secondary sexual characteristics can be made to approximate the normal The length of time required to obtain full androgenic effects is proportional to the duration of the eunuchism before therapy is started

The earliest effects of androgen treatment are noticeable very rapidly Increases in cutaneous blood volume and pigment are noted within an hour [6] *Spontaneous erections are very frequent during the first days of* treatment The general metabolic effects are readily apparent during the first weeks Gain in body weight is impressive and patients soon become aware of increasing muscular development Increased activity of the sebaceous glands results in augmented oiliness of the skin and hair Acne is a frequent development during the course of treatment The erythrocyte count hemoglobin and hematocrit rise The subject attains a sense of well being and many of his psychic disturbances abate An increase in the *basal metabolic rate parallels the improved body tone and stamina*

The Effects of Partial Loss of Testicular Androgen (Eunuchoidism) — In general males of this type manifest lesser degrees of subnormal somatic and sexual development than do eunuchs The range of patients is from those resembling castrates to those more like normal men If the testes are present in the scrotum they are small which is consistent with their reduced secretory function A variety of causes originating primarily in the testes or as a result of insufficient pituitary stimulation has been mentioned at the beginning of the discussion of testicular diseases The effects of eunuchoidism like eunuchism depend upon whether puberty had been completed before the onset of androgen insufficiency

Prepuberal eunuchoidism gives rise to the same type of eunuchoid habitus as that observed in prepuberal eunuchs Because some testicular androgenic hormone is present these subjects are apt to be taller than prepuberal castrates The very tall patients are also inclined to be thin although this is not a constant rule Varying degrees of genital underdevelopment are present depending on the magnitude of the hormone deficiency If ejaculation is possible the seminal fluid shows a marked reduction in the number of spermatozoa (oligospermia) if indeed they are present at all As a rule *spermatozoa are absent (azoospermia) and ejaculation is rare* Sexual desire and efficiency are usually markedly reduced All of the metabolic changes described for the eunuch may be observed in the more marked cases of eunuchoidism

Postpuberal eunuchoidism is not accompanied by the eunuchoid habitus and patients with severe hormonal deficiency resemble the postpuberal castrates The stature and voice of the mature adult are retained The accessory genitalia do not change much in size although the testes are small There may be a reduction in the growth of the body and facial hair but the need for shaving is usually not lost entirely There is some decrease of libido and sexual potency and symptoms of the male climacteric *may appear* The intensity of the metabolic effects is proportional to the extent of the androgen deficiency

Therapy of eunuchoidism should be started as early as possible Although the diagnosis is difficult in the *prepuberal or puberal boy* the absence of palpable testes or the presence of abnormally small testes should lead to the suspicion of pathologic hypogonadism If the testes are situated in the inguinal canal or abdominal cavity the patient should be treated as outlined in the subsequent discussion of cryptorchidism If and when recognized eunuchoidism like eunuchism should be treated at the age at which

puberty normally begins, *i e* at eleven or twelve years if irreversible eunuchoid skeletal changes are to be avoided. Even if the latter are present when the patient is first presented he can be strikingly benefited by therapy.

The type of therapy to be employed depends to a large degree upon whether the hypogonadal state is due to primary testicular insufficiency or is secondary to inadequate pituitary stimulation. The two types can usually be differentiated readily by assaying the gonadotropin content of the urine. An increased titer points to a primary defect in the testes whereas an absent or very low amount suggests that the adenohypophysis is at fault.

In the absence of facilities for hormone assays a therapeutic trial with gonad stimulating hormone may be helpful in determining whether the *eunuchoidism is primary or secondary*. It will also determine the subsequent management of the patient. A favorable response to the therapeutic test as indicated by genital growth means that the testes are not receiving adequate gonadotropin stimulation. On the other hand a lack of response signifies that the testes are hypofunctional due to intrinsic primary disease.

For the *therapeutic test* chorionic gonadotropin is employed since it contains predominantly the interstitial cell stimulating hormone (ICSH) which activates the Leydig cells to secrete androgen. Several commercial preparations of chorionic gonadotropin are available all prepared from the urine of pregnant women. The hormone is presumably secreted by the chorionic cells of the human placenta. Since these products are derived from humans there are no foreign protein antihormone reactions and they may be used over long periods of time. Intramuscular injections of 750 International Units twice daily for three weeks has been found by Heller and Nelson[270] to be an adequate test. If no response is obtained it can be safely assumed that the cause of the hypogonadism lies primarily in the testes themselves and that they are incapable of stimulation. In this event substitution therapy with androgens is indicated and should be administered as outlined at the end of this discussion.

A positive response elicited by the therapeutic test indicates that the patient should receive stimulation therapy with the same gonadotropin. A satisfactory and uniformly successful therapeutic regimen has been offered by Heller and Nelson[70] consisting of the intramuscular injection of 750 International Units of chorionic gonadotropin twice a day for four to six weeks. For the ensuing two months treatment is continued with one half this dosage. The patient is then allowed a rest period of from three to six months after which it must be ascertained whether the induced developmental changes have been maintained or have regressed. At times further development occurs after therapy has been stopped and spontaneous improvement may continue without any further treatment. When additional therapy is required three-month periods of treatment are alternated with three-month periods of rest. After a year or a year and a half of treatment many patients maintain their improvement indefinitely. This is possibly due to the resumption by the pituitary of gonadotropic activity in some manner as yet unexplained. The high degree of success and the frequently permanent results obtained with this schedule of therapy justify the large doses and frequent injections. Since twice-daily injections

may prove impractical, single daily doses of 1500 International Units may be employed instead

In patients whose testes have been deprived of adequate pituitary stimulation for a prolonged period of time Thompson [83] points out that irreparable testicular damage may occur Such patients may exhibit only a partial response to a therapeutic trial with chorionic gonadotropin since the testes are incapable of full stimulation Under these circumstances supplementary treatment with testosterone propionate is indicated even though the eunuchoidism is of the secondary type

Although therapy of the stimulation or substitution type can prevent or correct the manifestations of androgen deficiency in a given patient (except where a eunuchoid stature has already been established) neither type necessarily restores spermatogenic function Patients with a mild degree of eunuchoidism and arrested spermatogenesis may conceivably be restored to complete and normal gonadal function by endogenous or exogenous androgens However restitution to functional activity of a severely damaged germinal epithelium cannot occur as a result of ICSH stimulation or androgens alone For complete spermatogenesis to occur in seminiferous tubules potentially capable of responding the synergistic action of the follicle stimulating hormone would be required Unfortunately no highly potent pure preparation of FSH is yet available for this purpose

Where a follicle-stimulating effect is desired the gonadotropin contained in various extracts may be employed The use of human pituitary glands is obviously impractical and animal sources are utilized instead This involves the introduction of a foreign protein into the human organism and invites antibody formation Leathem [84] has recently reported the results of extensive observations on antihormone production using the various available gonadotropins Continuous therapy with commercial extracts of FSH derived from sheep and horse pituitary commonly lead to antihormone production The gonadotropin principle contained in the serum of pregnant mares (PMS)* also stimulates the formation of antihormone although this tendency is much reduced when purified low nitrogen preparations are employed The development of antihormones inhibits the action of the injected hormone on the target-organ and so reduces therapeutic effectiveness Maddock [85] has recently demonstrated that antihormones not only inhibit the action of the injected FSH but also neutralize the effect of the host s own pituitary gonadotropins That this is accomplished by the formation of an inactive hormone antihormone combination rather than by destruction is indicated by the continued urinary excretion of endogenous gonadotropins at a time when maximal amounts of antihormone are present in the plasma Apparently the kidney effects a separation of the hormone antihormone combination permitting the gonadotropin to be excreted while the antigonadotropin is retained Neutralization of endogenous pituitary gonadotropins by antihormones results in further

* The equine gonadotropin is secreted by the placenta of the pregnant mare and is unique in that it is not excreted in the mare urine although it is abundantly present in the serum Its properties are dissimilar from either pituitary or chorionic gonadotropin but its biologic actions resemble a combination of both FSH and ICSH predominantly the former

reduction in testicular function.[284] This undesirable effect can be prevented by interrupting treatment by a rest period after five to six weeks.

Allergic skin and constitutional reactions are quite uncommon although they may be serious and alarming. However, they do not interfere with clinical results since there appears to be no correlation between allergic reactions and the presence of antibodies.[287]

As mentioned previously, gonadotropin therapy is indicated exclusively in secondary hypogonadism where the testes are capable of responding. It is obvious that this form of therapy will be futile in instances of primary testicular deficiency where excessive amounts of circulating pituitary gonadotropin are already present. Patients with low levels of urinary gonadotropins, estrogens, androgens and 17-ketosteroids and with testicular biopsies showing immature, nonsclerosed tubules are the ones most likely to respond favorably.

The mode of administration of the follicle-stimulating type of gonadotropins is of utmost importance for successful results. Daily injections should be avoided since antihormones are more readily incited by frequent injections. Leathem[94] recommends weekly injections as being least apt to induce antihormone formation. The duration of effective therapy undoubtedly varies in different patients but should probably not exceed three months in any case. This should be followed by a three-month rest period since a second course of treatment is likely to induce antihormone production if given too soon. Rakoff[87] recommends alternation of gonadotropin preparations as a further measure in the avoidance of antihormonal responses.

Dosage schedules for the therapy of testicular hypofunction have not been adequately formulated. In general, 500 to 1000 International Units* is the recommended individual dose.

When the testes are found to be nonresponsive to the therapeutic test with chorionic gonadotropin, replacement therapy in the form of androgenic preparations must be employed. *Testosterone propionate, 10 mg in oil*, may be injected intramuscularly 3 times a week. In patients whose hormonal deficiency is more marked, larger doses approximating 25 mg 3 times a week may be required. When it is apparent that a long range therapeutic program will be in order, it is advisable to implant subcutaneously 6 or 8 pellets of *testosterone*, each weighing about 75 mg. This provides a maintaining effect for from three to six months. The oral administration of methyltestosterone is also a satisfactory method employed in androgenic therapy. Since the dose must be 4 to 6 times the corresponding dose of testosterone propionate, weight for weight, a dose of 1 to 2 25 mg tablets daily yields the same androgenic effects as approximately 10 to 25 mg, respectively, of the propionate injected 3 times a week.

Pseudo-eunuchoidism is a term which has been applied by McCullagh[169] to describe a group of patients with certain clinical features that suggest eunuchoidism but who in fact have no evidence of androgen deficiency. These men have a rather boyish beardless face, very scant axillary and chest

* Equine gonadotropin is standardized so that one I U is equivalent to the specific gonadotropic activity of 0 25 mg (250 gammas) of the standard preparation in possession of the Health Organization of the League of Nations. For purposes of comparison 20 I U represents one Cortland Nelson rat unit.

hair and high pitched voices. The genitalia are usually normal, as are the pubic and leg hair. Normal numbers of spermatozoa with good motility are present in the ejaculate. The skeleton is of the mature type and the urinary excretion of androgens, 17-ketosteroids and gonadotropins are within normal limits. The administration of large quantities of testosterone is virtually without effect in contrast to the readily obtainable hair and voice changes in ordinary eunuchoidism with the same treatment. McCullagh believes this group to belong in the general class of congenital disorders. It is quite probable that the deficiency in these cases lies not in hormone production but in end-organ response. The voice mechanism and the dermal apparatus involved in hair growth apparently have an above normal threshold of response to androgenic stimulation.

Conditions characterized by failure of an end-organ to respond to its own hormone have been classified in Albright's laboratory as instances of the *Seabright bantam syndrome*.[288] The expression is derived from the fact that the male Seabright bantam has female feathering. This is presumably due to the fact that the feathers of this species of male bird respond in an abnormal way to the normal male hormone.

Other examples of end-organ failure include pseudo-hypoparathyroidism[88] in which normal amounts of parathyroid hormone are secreted by normal parathyroid glands but a hypocalcemia is present due to the failure of the tissues to utilize the hormone. Additional examples are represented by the beardless American Indian and by certain individuals who have a very low basal metabolic rate without evidence of hypothyroidism. In none of these instances is there a deficient hormone production despite the presence of clinical findings that would ordinarily suggest it.

The Klinefelter Reifenstein Albright Syndrome.—Popularly called the Klinefelter syndrome, this clinical entity was described in 1942.[144] It represents the first clear-cut correlation between hypogonadism, hormonal assays and testicular biopsy examinations. The authors reported a group of 9 men ranging from seventeen to thirty-eight years of age with gynecomastia, very small testes, azoospermia and increased amounts of urinary gonadotropin. Histologic examination of testis tissue obtained by biopsy showed varying degrees of tubular lesions consisting of partial to complete hyalinization with loss of spermatogenesis. The testicular lesion was regarded as being confined entirely to the tubular epithelium since the interstitial cells of Leydig appeared numerous and prominent in all sections. The fact that the Leydig cells were intact was consistent with the observation that all but one of the patients had well-developed accessory sexual organs; all were strong and muscular and axillary, pubic and perineal hair was normal. Several had recession of the hair above the temples which is evidence of good Leydig cell function. The breasts were bilaterally enlarged and showed some enlargement of the areola but very little increase in pigmentation. No secretion was present. Histologic examination showed a marked proliferation of the periductal connective tissue with some hyperplasia of the ductal epithelium. This was noted to be in contrast with the breast findings occurring in estrogen induced gynecomastia of elderly males. In these cases a considerably greater proliferation of the ductal epithelium occurs with much less periductal fibrosis.

Although the authors emphasized the preservation of androgenic function in the majority of these patients, it is noteworthy that eunuchoidal skeletal changes were present in each case. The arm span was greater than the height in every instance. Bone age was delayed in one individual, and 3 of the younger patients (aged seventeen to twenty-eight years) did not shave. In one instance the findings included a high pitched voice, small larynx, sparse beard, small penis and a small prostate. A complete aspermia with lack of ejaculation was occasionally noted in this group. The urinary excretion of 17 ketosteroids was usually decreased and the extent of the reduction paralleled the degree of hypoleydigism.

Since the patients stated that the testes were always small and the gynecomastia began shortly after puberty, the onset of the disease can be dated to adolescence. This is confirmed by the eunuchoidal body proportions in which the arm span exceeded the height.

The original classical description by Klinefelter and his coworkers has been extended by Heller and Nelson[4, 68, 59] to include a larger group of men with hypogonadism. They term this enlarged group "puberal seminiferous tubule failure" and regard it as the most common form of gonadal failure and yet the least often recognized. Within a period of one year they were able to identify and study completely 20 men having certain characteristics in common which justify their inclusion in this category. According to their concept gynecomastia is not a constant finding and occurs primarily in those patients who manifest the least, if any, evidence of androgen deficiency or eunuchoidism. On the other hand, a moderately or markedly eunuchoidal group of patients having identical testicular tubular lesions, small testes and increased urinary gonadotropins often have no gynecomastia. Rather than designate this hypoandrogenic group of patients as a new syndrome distinct from that described by Klinefelter *et al*, it is more rational to specify a broader type of hypogonadism characterized by certain *constant* features in addition to several *variable* findings.

In order to be included in this syndrome a characteristic histologic picture must be present in the testes. Fibrosis of the seminiferous tubules is the dominant lesion and is usually recognizable in various degrees. The earliest lesion is a thickening of the basement membrane and lamina propria of the tubule. As the process advances one finds widespread sclerosis of the tubular structures, the end result of which is a complete or nearly complete hyalinization of all the tubules. The tubular pathology does not develop at a uniform rate so that quite often a single testicular section reveals several different stages of fibrosis. Small atrophic completely hyalinized tubules may be found alongside tubules which still contain epithelial cells. Some tubules may even show spermatogenesis, while others may be lined exclusively by Sertoli cells. Other tubules may reveal arrested spermatogenesis and considerable peritubular fibrosis with fibrosis of the lamina propria. The Leydig cells are quite prominent and often give the appearance of being increased in number. This is often more apparent than real and is largely due to the shrunken state of the adjacent tubules. The interstitial cells of Leydig characteristically appear in clumps. When clumping is marked, coalescence of such aggregates simulates adenoma formation. It has been claimed[4] that the Leydig cells show a tendency to decreased

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granulation which can be correlated with the fact that all patients in this group manifest some degree of hormonal deficiency, however slight Abnormalities of the Leydig cells have also been reported by Howard and his coworkers [146] These include a lack of maturation abnormal cell forms with degeneration and absence of cytoplasmic secretory changes However a satisfactory correlation between the morphologic appearance and functional activity of Leydig cells has not been conclusively established

As a result of the pathologic changes in the testicular tubules, both testes are small and usually quite firm When ejaculation is possible semen analysis discloses a complete azoospermia Since the cause of the hypogonadism in these patients is located in the testes proper the urinary gonadotropins are increased above normal often to levels ordinarily found in castrated men

In addition to the constantly present features just described there may be other manifestations present to variable degrees in different patients *Gynecomastia*, originally described as an integral part of the syndrome, is often absent In this connection one must be careful to distinguish pseudogynecomastia which frequently occurs in obese eunuchs and eunuchoids, *and merely consists of a feminine distribution of fat in the mammary* region [90] In these cases the breast enlargement is also bilateral but there is no actual hypertrophy of breast tissue When true gynecomastia develops in these patients it is bilateral occurs at or shortly after puberty progresses for some years and then becomes stationary There is some increase in the size of the nipples and areolæ but no secretion is present As previously mentioned Heller and Nelson [68] found gynecomastia primarily in those subjects who manifest little or no gross evidence of androgen deficiency However, in a recent report of 30 cases Howard and his coworkers[146] could not confirm this association Breast enlargement was absent in 5 out of 20 men in their non eunuchoidal group It is sometimes difficult to be certain whether true mammary gland enlargement is present especially in the obese subject In these instances one must rely on the characteristic glandular consistency which is best palpated in the subareolar region The evaluation of breast enlargement in the pubescent male is also very difficult at times since a certain amount of mammary hypertrophy is almost physiologic at this period However one may be guided by the fact that important breast enlargement rarely persists beyond the age of seventeen or eighteen years [91]

The histologic appearance of the breast in gynecomastia is characteristic It will be recalled that the normal male breast has a relatively small number of ducts lined by low cuboidal epithelium and surrounded by a moderately dense collagenous stroma alveoli are rare or absent In contrast the breasts of patients with gynecomastia show a marked increase in the amount and density of the periductal stroma with some new duct formation The ductal epithelium is taller than normal and may reveal some hyperplasia The preponderance of the stromal over the ductal reaction is in marked contrast to the findings in gynecomastia which has been induced by stilbestrol In these cases the effect is principally on the duct system with considerable hyperplasia and stratification of the lining epithelial cells at times intraductal proliferations or buds may be seen The

cause of the gynecomastia as it occurs in the Klinefelter syndrome has not been satisfactorily explained. Klinefelter and his associates attribute it to a loss of "inhibin" (a hypothetical estrogen-like secretion of the seminiferous epithelium) which permits the mammogenic action of the androgenic hormone to proceed unopposed. Since the existence of a second testicular hormone has not been conclusively established, its involvement in the etiology of gynecomastia is still a matter of speculation.

Inconstant but frequently present manifestations include varying degrees of *androgen insufficiency*. The habitus of the subject may range from almost normal (except for gynecomastia and subnormal hair growth) to definitely eunuchoidal. In the latter event the typical eunuchoidal skeletal configuration may be present, the external genitalia may be infantile (although libido, erections and ejaculation are often present) and the pitch of the voice may be high. Hair development on the face, torso, axillae, pubes and extremities may be sparse or absent. Muscle power may be diminished. Symptoms of the male climacteric were noted by Heller and Nelson [59] in all patients by the time they reached the age of twenty-five years. The urinary excretion of 17-ketosteroids and estrogens may be reduced. The extent to which the clinical picture of eunuchoidism develops depends upon the degree of Leydig cell failure. The clinical appearance is also modified by whether or not puberty had been completed at the time the testicular secretory function became impaired.

It must be emphasized that although tubular lesions and failure are invariably present, there is usually in addition some accompanying degree of androgen deficiency. In younger subjects this may not be readily apparent. Interestingly enough, all but 2 of the 60 cases reported in the literature have been under forty years of age. Since this disease is not characterized by spontaneous remissions and the testicular lesions are probably progressive as is suggested by the early appearance of climacteric symptoms, it is not unreasonable to anticipate total secretory failure in certain older patients. Under these circumstances it is possible to hypothecate eventual disappearance of the Leydig cells in some cases. Such a mechanism might explain certain instances of eunuchoidism of obscure etiology in older men.

If one accepts the theory of subfunctional Leydig cells as an integral part of this syndrome, it is possible to explain the increased urinary excretion of gonadotropins in all patients. This would depend upon a difference in the threshold of response between the adenohypophysis and the accessory sexual end-organs whereby the former is more sensitive than the latter. A slight decrease in the amount of circulating testicular androgens might account for an increased gonadotropic activity of the anterior pituitary before it causes end-organ failure.[68] This mechanism would preclude the invocation of the "inhibin" theory by which a loss of inhibitory effect on the anterior pituitary is said to permit excessive gonadotropic activity. A third alternative explanation for the increased urinary gonadotropins omits the need for hypothetical considerations involving differential tissue sensitivity and a second testicular hormone. It postulates a rise in gonadotropin titer merely as a result of failure or inability of the seminiferous tubules to utilize the follicle-stimulating hormone.[68] However attractive, none of these concepts has been conclusively proven and the cause

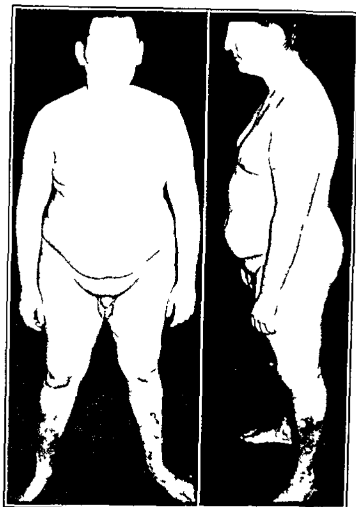


Fig. 39.—Appearance of a 25 year old man with Klinefelter's syndrome described in the text. *Apparent are gynecomastia, small penis and testes, female type of pubic hair* (overhung by the abdominal panniculus), sparse facial hair, obesity and wide hips. The arm span exceeds the height by one inch.

of the increased gonadotropic content of the urine of these patients awaits further study and clarification.

The cause of the Klinefelter syndrome is unknown. It is most likely due to a constitutional defect having a predilection for the seminal epithelium. A remarkable familial trend has been reported by Reifenstein.[9] The syndrome was found in 9 out of 10 members of one family in two generations. There was some evidence to indicate that the effect was transmitted by the female sex.

The clinical and laboratory findings in a typical case of the Klinefelter syndrome are well illustrated by a patient from our Endocrine Clinic.

Illustrative Case

A twenty five year old unmarried white male was admitted because of swollen breasts. This was his only complaint and was a source of considerable self consciousness and shame. Breast enlargement was first noted at

about the age of ten years. Penile erections occurred at intervals but coitus and nocturnal emissions were denied. Shaving had never been required and axillary and pubic hair appeared at about the fifteenth year. There were no significant antecedent illnesses including mumps or overt evidence of testicular disease. A gain of 50 pounds in weight occurred during the previous two years. Physical examination disclosed a marked truncal obesity involving principally the girdle area about the hips and lower abdomen. The breasts were markedly enlarged and glandular tissue could be palpated apart from the mammary fat deposits. A minimal amount of soft hair was present in the mustache and beard region of the face. The pubic and axillary hair was normal in amount although the former presented the female type of escutcheon. Cranial hair was abundant and silky. The testes were small and atrophic. The penis was subnormal in size and the prostate was markedly hypoplastic. The voice was masculine in quality. The patient's height was 64½ inches and his arm span was 65½ inches. The chest measured 38 inches in expiration, 39½ inches in inspiration and his girth at the level of iliac crests was 44 inches.

Roentgen examination disclosed a normal sella turcica and no delay of epiphysial closure in the long bones or iliac crests. The basal metabolic rate was +4 per cent and the glucose tolerance test was within normal limits. The assay for urinary gonadotropins was positive at 60 and negative at 80 mouse uterine units which represents a distinct increase above normal. The method employed in our laboratory is a slight modification of that described by Klinefelter, Albright and Griswold and Smith, Albright and Dodge and gives the upper limit of normal at 40 to 50 mouse uterine units. The urinary excretion of neutral 17-ketosteroids was 9.0 mg. per 24 hours which is toward the lower range of normal.

Histologic examination of a section of testis tissue removed by biopsy revealed advanced fibrosis of most of the seminiferous tubules with complete disappearance of the epithelial elements. Leydig cells were present in conspicuous numbers. The microscopic appearance of a specimen of breast tissue removed by biopsy was that of extensive periductal fibrosis. The ducts were few in number and showed slight hyperplasia of the lining epithelium.



Fig. 40. Testicular biopsy from a 27 year old man with Klinefelter's syndrome. Histologic examination shows varying degrees of atrophy of the seminiferous tubules. The small segments (at the left) are completely fibrotic and hyalinized. Others show less advanced changes with a marked decrease in the number of gametogenic cells. Of the germinal elements only spermatogonia and primary spermatocytes are present. Sertoli cells are frequent. The lamina propria surrounding the tubules is moderately thickened. Clusters of Leydig cells are recognized as dark cell masses to the right and left of the center. H & E stain (× 160).

present in the condition known as ovarian agenesis[295,296] or Turner's syndrome.[328] Compromise of testicular blood supply during operative procedures in this region and bilateral morbid processes resulting from trauma, inflammatory disease and malignancy are additional factors capable of causing complete testicular atrophy.

Therapy is that previously described for eunuchism and is necessarily substitutional since the testicular substrate is incapable of stimulation. Testosterone propionate, 25 mg. in oil, is administered intramuscularly 3 times a week. Since replacement treatment must be continued throughout life, the subcutaneous implantation of testosterone pellets is preferable and more convenient. Six to 8 pellets, each weighing 75 mg., will maintain adequate androgenic stimulation for three to six months depending on the rate of absorption.

Cryptorchidism.—The testes normally descend into the scrotum shortly after birth. Failure of descent may be due to mechanical obstruction in the inguinal canal or to hormonal dysfunction. The endocrine mechanisms involved in causing testicular descent are not clear. The observations of Engle[71] in the monkey suggest that gonadotropins, especially the interstitial cell stimulating type of placental origin, may play an important role in humans. It is highly probable that an increased output of androgen by the stimulated testis is an additional factor in favoring descent. This may be deduced from observations in the experimental animal[132] indicating that descent is preceded by an increase in the size and weight of the gonad as well as by enlargement of the accessory genital structures (scrotum and spermatic cord).

A cryptorchid testis is one which at no time has entered the scrotum. It may be situated just outside the external inguinal ring in the puboscrotal region or it may be retained within the inguinal canal or the abdominal cavity. Towsley[10] estimates the incidence of undescended testis to be 1 out of every 25 to 30 boys under fourteen years of age. In men above the age of twenty one years it is much less frequent, occurring once in 400 subjects. It is therefore obvious that the majority of testes which are not descended at birth or during childhood undergo spontaneous descent at the time of puberty. Cryptorchidism is usually unilateral and is said to occur more frequently on the right side. Unilateral cryptorchidism is much less likely to be due to endocrine factors than is the case with bilaterally undescended testes.

When one or neither testis can be felt in the scrotum it is important, in the first place, to be certain that true cryptorchidism actually exists. It is necessary to distinguish between genuine retention and false or intermittent retention (pseudocryptorchidism). The latter is common in children and due to facile contraction of the cremasteric muscles which pull the testes up toward the inguinal region. It is often essential to secure adequate relaxation of these muscles as well as the child who frequently becomes frightened and tense while his genitals are being examined. The boy should be asked to lie on his back with his legs apart. A hot water bottle is applied to the scrotal area and the body is kept warm with a blanket. It may require as long as one half hour to obtain the subject's confidence and relaxation. Examination should be gentle and brief although it may be necessary to repeat this procedure several times in order to overcome

the cremasteric reflex. If the testis cannot be palpated it is then advisable to apply pressure to the lower abdomen in the direction of the inguinal canal. This maneuver may result in forcing the testis into the scrotum; such a testis is not truly cryptorchid and requires no treatment.

Once established, the diagnosis of cryptorchidism presents the patient with certain hazards. Spermatogenic function becomes destroyed if the testis remains out of the scrotum after puberty.[46, 97] Histologically, the seminiferous tubules retain their immature state and eventually may become atrophic or sclerotic. Hence a bilaterally cryptorchid male remains infertile. Furthermore there is evidence that long-continued cryptorchidism may eventually result in a slight decrease in secretory (androgenic) function.[1, 3] An increased urinary excretion of gonadotropins has also been

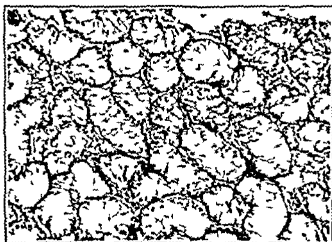


FIG 42 — Testicular biopsy from a 13 year old boy with bilateral cryptorchidism. The seminiferous tubules are of the infantile type. They are small, closely set and contain no lumen. The lamina propria is distinct but not thickened. The lining epithelial cells consist generally of a single layer of primitive spermatogonia. Sertoli cells are absent and the intertubular tissue contains no Leydig cells. H & E stain (× 200)

noted in cryptorchid men,[109] although further studies are desirable to clarify the significance of this finding. On the other hand, very reduced or totally absent urinary gonadotropin titers are occasionally present. These point to an endocrinologic cause for the cryptorchidism such as hyposecretion of pituitary gonadotropins.

Of considerable importance is the frequency with which malignant testicular tumors are found in retained testes. Gilbert and Hamilton[73] noted that approximately 11 per cent of more than 7000 malignant testicular tumors occurred in men with ectopic testes. This proportion is about 50 times greater than can be accounted for by chance. Twombly[81] studied a series of teratoma testis and recorded an incidence of about 13 per cent in men with cryptorchidism. Both of these studies point out the fact that the tumor may involve the normally descended testis in some cases. It is to be emphasized that tumor formation usually occurs some time after puberty and is not an important consideration during childhood.

Because of eventual interference with testicular function and the possibility of involvement by neoplasm the *management* of ectopic testis merits serious deliberation The problem is somewhat different in the child than it is in the adult and will be considered first

Although it is universally accepted that an undescended testis should be in the scrotum at the time of puberty there is a wide divergence of opinion concerning the optimal time for treatment of uncomplicated cryptorchidism in the prepuberal male Since cryptorchidism may co-exist with evidences of primary or secondary hypogonadism indications for therapy in such cases are determined by the nature of the underlying endocrine disturbance No effort will be made to survey the pertinent extensive literature which has been exhaustively reviewed by Bishop [300] The various therapeutic approaches include three principal avenues The first is to do nothing in view of the fact that the majority of cryptorchid testes descend spontaneously at puberty In this way needless endocrine treatment and meddlesome surgical interference can be avoided However there is a wide individual variation in the age at which puberty may begin and a course of watchful waiting may result in testicular tubular damage if delayed too long Therefore definitive action should be taken before the effects of puberty become too well defined

A second therapeutic consideration is the use of endocrine products which are employed by many workers This consists of the administration of chorionic gonadotropins (containing predominantly the interstitial cell stimulating hormone) and androgens The latter is not used alone and is of dubious value since most reports have been discouraging [301] The effectiveness of chorionic gonadotropins was first demonstrated by Engle[71] and many favorable reports of its clinical efficacy have been published [30, 303] Thompson[304] is of the opinion that when chorionic gonadotropin therapy induces testicular descent it would have occurred spontaneously at puberty without treatment Advocates of endocrine therapy base their contention upon the following considerations (*a*) a mechanical barrier can be assumed if therapy is ineffective indicating that surgical interference will be required (*b*) even if descent is not achieved enlargement of the genital organs (scrotum and spermatic cord) facilitates the subsequent operative treatment If endocrine therapy is to be employed it should be administered between the ages of seven and eleven years The suggested initial dose is 100 International Units 3 times a week This may be increased in a few weeks to 300 or 500 International Units thrice weekly until the testicle is in the normal position If a positive response is obtained this will occur in a few weeks to several months Total dosage should rarely exceed *10 000 to 12 000 I U Therapy should be discontinued if undue* stimulation of the accessory sex organs occurs

It is to be emphasized that many experienced observers recommend no endocrine therapy in uncomplicated prepuberal cryptorchidism [307, 306] In the absence of definite evidence of hormonal insufficiency it is held that endocrine treatment has no sound rationale Under these circumstances it is advised that the boy be given every opportunity for spontaneous descent If a normal position is not attained early in puberty the problem promptly becomes a surgical one and orchiopexy is recommended Heller

and Maddock,[306] recognizing the variable onset of puberty in normal children have adopted a physiologic end point for the beginning of puberty, namely, the development of the penis and scrotum and the appearance of pubic hair. If these signs of puberty appear unaccompanied by testicular descent, it is assumed that the organ is being mechanically retained. Orchiopexy should be delayed no further because of the danger of seminiferous tubular damage.

However, this program warrants a note of caution to which attention was called above in connection with the problem of delayed puberty. Since it is often difficult to differentiate between physiologically late and pathologically absent signs of maturity, irreversible eunuchoidal changes may *occur during a prolonged period of expectant observation*. For this reason treatment of uncomplicated delayed puberty should not be deferred beyond the sixteenth year. When cryptorchidism and its inherent danger of spermatogenic damage is present, it is inadvisable to withhold therapy, endocrine or surgical, after the age of eleven years.

The presence of congenital inguinal hernia on the same side as the undescended testis constitutes a definitive surgical indication. In this event a combined orchiopexy and hernioplasty should be performed whenever the diagnosis is made, preferably before the age of eleven years.

As mentioned previously, the management of cryptorchidism *in the adult* presents a different problem. Atrophy of the retained gonad with impairment of spermatogenic function has already taken place. The likelihood of tubular regeneration following surgical fixation in the scrotum varies directly with the length of time it had been situated ectopically. Ectopic retention for several years after puberty virtually precludes restoration of gametogenic function. A more important consideration is the greater incidence of malignant degeneration in undescended than in descended testes. This raises the question as to whether the atrophied testis should be preserved since malignant tumors have been reported to develop in atrophied testes some years after they were placed in the scrotum by surgical fixation.[307,308] In general the younger adults should be treated by orchiopexy. The hopelessly atrophied testis of older cryptorchid men is advisedly sacrificed *except when the condition is bilateral. Under these circumstances* a compromise must be reached between the psychic and metabolic repercussions of total castration and the much less common danger of malignant transformation. In these cases it may be preferable to resect one (the smaller if there is a difference) and fixate the other in the scrotum.

After surgical correction of cryptorchidism has been accomplished the subject should be observed to ascertain whether the testis is functioning properly. If evidence of gonadal failure becomes apparent endocrine therapy should be instituted. Stimulation with chorionic gonadotropin is the *treatment of choice in the beginning. Dosage requirements will vary* according to the extent of hypogonadism but average about 500 International Units 3 times a week. In the more marked cases 1500 International Units daily may be necessary. If stimulation therapy fails replacement treatment with testosterone will be indicated.

Male Infertility.—This category includes only those cases having gametogenic failure of the testes without involvement of the secretory function

As stated in many previous sections, Leydig cell failure soon becomes associated with germinal cell failure because seminal epithelial function depends upon actively functioning Leydig cells. Hence males with androgen deficiency are also infertile but their sterility is overshadowed by clinically overt manifestations of hypogonadism. These patients are not included in the group here discussed.

Most men with simple infertility seek medical attention because of a barren marriage and have no endocrine disturbance. The testes are usually quite normal, potentia and ejaculation are unimpaired (except when affected by psychological factors) and the seminal fluid usually shows a reduced number of spermatozoa (oligospermia) or no spermatozoa (azoospermia). An increased number of abnormal sperm forms may be present. A detailed discussion of the entire subject covering methods of investigation, etiologic factors and management has been ably presented by Hotchkiss.[7]

Since patients in this category usually disclose no manifestations of endocrine deficiency and only infrequently any previous history of identifiable etiologic factors, one can only speculate as to basic causes. Nelson and Heller[168] believe that several different factors can produce the same condition. These may include vascular changes in the testes, episodes of nutritional and vitamin deficiency, subclinical inflammatory testicular disease or constitutional defects having a particular predilection for the seminiferous epithelium.

A rational and effective approach to the problem of male infertility requires the combined efforts of the urologist, the internist, the pathologist and the endocrinologist. Much of our knowledge concerning the infertility of man has been developed during the past decade, beginning with the pioneer work of Hotchkiss[77] and Charny.[272] These workers demonstrated the simplicity and usefulness of the testicular biopsy which soon proved to be the best single adjunct in the appraisal of fertility. Its use in conjunction with semen analysis constitutes the spearhead of our investigative attack against male sterility.

Following its introduction as a diagnostic procedure in 1940, testicular biopsy became extensively applied to the elucidation of all types of hypogonadism as well as to the problem of male infertility. It is only with the latter that we are concerned here. Notable contributions to our current knowledge of testicular histopathology as it occurs in the infertile male have been made by Hotchkiss,[77,309] Charny,[272,310,311] Charny and Meranze,[6] Engle[312,313,314] and Simmons and Sniffen.[315]

Testicular biopsy is indicated in any given case only after semen analysis has definitely established the existence of a substandard spermatozoan pattern. The finding of impaired quality of the seminal fluid on one examination is not accepted as final since certain factors may introduce errors in interpretation. These include loss of part of the ejaculate, especially the first portion which contains most of the sperm, and immediately antecedent excessive sexual activity which may reduce the sperm count.

Microscopic examination of the testes should include both gonads. Since both testes contribute to the sperm content of the semen, a unilateral testicular lesion does not affect the fertilizing capacity of the individual

Unless *both* testes are found to be involved it is impossible to regard a disturbance in a *single testis* as responsible for sterility.

Testicular biopsy not only identifies defective spermatogenesis but excludes cases with Leydig cell involvement which do not properly belong in this group. Histologic examination is of further value in that the finding of normal or relatively normal spermatogenesis signifies that the trouble lies not in the formation of sperm but in their transport. Inflammatory or congenital occlusion of the duct system accounts for approximately one-third of all male infertility problems. It is important to recognize these cases since they are occasionally amenable to surgical procedures designed to establish free continuity of the ductal channels.[77]

The histologic characteristics of the seminiferous tubules in the type of infertile male under discussion are quite variable and often very difficult to interpret. In a general way the testicular morphology can be correlated with the seminal fluid analysis but there are many exceptions. Classification of the tubular findings on a clinico-pathologic basis has been made by Charny[311] in a group of 263 patients. He divides them into:

1. *Developmental lesions*, occurring in 18 per cent, due to failure of maturation. The tubules are smaller than normal and surrounded by an increased amount of connective tissue. The basement membrane is neither thickened nor shrunken. These lesions are usually found in cryptorchidism and in hypogonadism due to prepuberal hypopituitarism. The latter condition is a distinct endocrinopathy and is ordinarily not included in the category of male infertility under discussion.

2. *Degenerative lesions* found in 46 per cent, occurring in tubules which had already matured. The tubules may be reduced in size but generally are not. The basement membrane may be wavy when the tubules have shrunk or it may be thickened. Nutritional, toxic and postpuberal endocrine disturbances may be causative factors in this group.

3. *Inflammatory lesions* noted in 36 per cent, characterized by fibrosis varying from minute thickening of the basement membrane to a point where the band of dense connective tissue surrounding the tubule is wider than the tubule itself. Intertubular fibrosis and inflammatory cell infiltrations may also be found.

Conceding the difficulties inherent in classification on a morphologic basis, Engle[312] has offered a grouping of lesions encountered in cases of *azoospermia* of gonadal origin. The patients were drawn largely from a sterility clinic where the primary complaint was involuntary childlessness. Eunuchoidism and other systemic manifestations of hypogonadism were present in only a minority of cases.

1. *Tubular fibrosis* when marked leading to atrophy of the tubule. This begins as a thickening of the lamina propria due to laminization and hyalinization of the collagen fibers. The basement membrane is also thickened but to a lesser degree. The epithelial cells may become atrophic and denuded and finally disappear leaving only Sertoli cells lining the tubules. Because this lesion is found in young men but also with increasing frequency in successive decades, this has been termed *progressive* tubular fibrosis. There is no known cause for this lesion which is presumably not on an endocrine

or nutritional basis. It is also probably an irreversible change due to its fibrous character which would render treatment futile.

2. *Germinal aplasia* is evident in tubules showing a complete absence of germinal epithelium. Sertoli cells are present, the tunica propria is not thickened and the tubules themselves are moderate in size. It is occasionally found in cryptorchid testes of late adolescents. Usually there is no demonstrable cause, although a history of exposure to radioactive agents is obtained at times. It is of interest that Leroy[316] found identical lesions in men after exposure to the atomic bomb explosions in Hiroshima and Nagasaki. There is no therapy for this type of tubular lesion which has been likened by Engle[314] to analogous situations in the female where absence of germ cells results in ovarian agenesis.[29, 96] It is to be noted, however, that any possible analogy does not extend beyond a morphologic one. Endocrine manifestations are said to be absent in males with germinal aplasia while they are abundant in women with ovarian agenesis; these patients have a well-defined ovarian hormonal deficiency invariably associated with increased amounts of urinary gonadotropins. Urinary gonadotropins have been reported to be normal,[117] moderately elevated[146] or greatly increased[317] in testicular germinal aplasia.

3. *Spermatogenic arrest* characterized by numerous spermatogonia which proliferate to the primary spermatocyte stage with no further maturation. The Sertoli cells and lamina propria are unaffected. There are no recognized etiologic factors or effective therapy for this condition.

Three histologic variants are commonly encountered in *oligospermia* of gonadal origin.[313]

1. *Spermatogenic arrest* at a higher level in the process of spermatogenesis so that in some tubules a small number of mature, often deformed spermatozoa are released.

2. *Defects of nuclear structure and cell division* have been found in a considerable number of men whose sperm counts show a high percentage of abnormal spermatozoa. The tubules are normal in size and contour and show no fibrosis. Abnormalities are sometimes seen in division of spermatogonia. Atypical mitoses are especially common in the primary spermatocytes where multinucleated cells are frequently noted. Normal secondary spermatocytes are rare and there is much pyknosis and cytolysis. The resulting spermatids have abnormally shaped nuclei. A disturbance in chromosomal mechanism rather than in endocrine function is the likely basis for these findings.

3. *A general reduction in the proportion of all elements of the spermatogenic series.* The tubules are essentially normal and all stages of normal spermatogenesis are present but in reduced numbers. The appearance is that of a general retardation of spermatogenic function. This defect may be referred to as "hypospermatogenesis" and may conceivably be benefited by endocrine stimulation. However, no clinical data are yet available to evaluate this possibility.

It is to be emphasized that epithelial and fibrotic changes do not affect all tubules equally. Local areas of degenerated tubules may be interspersed among relatively normal tubules. Conversely, islands of relatively intact tubules may be found in otherwise degenerated tissue. The presence of

peritubular fibrosis beginning with thickening and hyalinization of the lamina propria is always an indication of injury to the basally situated gametogenic cells. The question as to whether the fibrosis or the epithelial damage is the primary factor has not yet been settled. Sand and Okkels[3] maintain that the fibrotic lamina propria damages the contained epithelial cells by interfering with their nutrition. The opposite view is held by Charny and Meranze,[4] who claim that the connective tissue changes are secondary to a primary lesion in the tubular epithelium.

Diagnostic investigation along endocrinologic lines is usually not of much assistance in the evaluation of patients who complain only of infertility. Deviations from the normal urinary hormonal pattern are seldom encountered. *When present they are usually accompanied by other* clinical and laboratory evidence of endocrine dysfunction. In the great majority of cases the urinary gonadotropin is normal. Marked elevations have been reported in cases with complete tubular germinal failure.[217] The increased urinary gonadotropins are said to be in direct proportion to the number of tubules which are hyalinized or lacking in germinal epithelial elements. In general, however, the presence of increased urinary gonadotropins usually signifies an associated eunuchoidism of primary testicular origin. Markedly reduced or totally absent urinary gonadotropins is evidence of primary pituitary failure and is usually not encountered in the group of patients under discussion.

Because of the incomplete state of our knowledge the physician concerned with prognosis and therapeutics is often at a loss in the management of the infertile male. *Nevertheless the fund of data currently available* provides certain guiding generalizations. Infertility due to deficient androgen production comprises but a small part of the problem of the sterile man. It is usually readily recognizable by the accompanying overt clinical manifestations of hypoandrogenism and to a lesser extent by urinary hormonal assays for gonadotropins, androgens, neutral 17-ketosteroids and estrogens. Testicular biopsy is also of assistance in the evaluation of Leydig cell function.

The *majority of patients complaining only of sterility have no demonstrable underlying endocrine disturbance.* Furthermore, known etiologic factors such as cryptorchidism, orchitis, trauma, exposure to radioactive agents and nutritional deficiencies account for but a small proportion of cases. This leaves us with a fairly large group of patients in whom the matter of therapeutic procedure is largely conjectural. It is in this group that histologic examination of testicular tissue is most useful. The finding of completely atrophic tubules, germinal aplasia or spermatogenic arrest at the *primary spermatocyte stage indicates an irreversible lesion.* The prognosis is hopeless and therapy will be of no avail. Peritubular fibrosis with thickening of the lamina propria is also generally regarded as therapeutically irreversible.[6,210] This is undoubtedly true in the vast majority of cases although attention should be called to 2 cases in which similar lesions almost completely disappeared after endocrine therapy. The first is a seventeen year old boy described by McCullagh[169] with hypogonadism due to a pituitary adenoma. Extreme tubular atrophy with replacement fibrosis was *present in testicular sections. After removal of the pituitary tumor,* irradia-

tion of the pituitary region and the administration of 500 I U of anterior pituitary-like hormone (ICSH) 3 times weekly for six months somatic and sexual maturity was markedly stimulated Testicular biopsy at this time showed a striking improvement in tubular structure with a remarkable clearing of the fibrotic process

The second illustrative patient was described as Case 12 in the group of men with idiopathic eunuchoidism-with low-FSH' reported by Howard and his coworkers [146] This was a nineteen year old man with a character istic eunuchoid habitus whose testes showed a marked thickening of the tunica propria without peritubular proliferation Seminal epithelial mat uration was only slight and there were no Leydig cells One and one half years later after 1050 mg of testosterone by subcutaneous implantation there was decreased thickening of the tunica propria and increased matura-tion up to the stage of primary spermatocytes Leydig cells were still absent

Although these 2 cases offer a ray of hope in the management of patients with seminal tubular fibrosis the results with endocrine therapy are, for the most part very discouraging [310] In any event endocrine therapy should be reserved exclusively for those patients in whom a definite hor monal deficiency can be established

The histologic demonstration of hypospermatogenesis, a condition char acterized by the presence of all of the normal elements of spermatogenesis but in reduced numbers offers promise of successful endocrine therapy This may also be a likelihood in those patients with oligospermia who show spermatogenic arrest at the spermatid stage Insufficient cases have been studied and reported to throw light on this therapeutic possibility Evi dences of associated deficiency are usually lacking so that precise thera peutic indications along this line are absent Nevertheless the empiric use of hormonal agents to stimulate the sluggish germinal epithelium is in order This involves intramuscular injection of equine gonadotropin (PMS) derived from pregnant mare serum which possesses an active follicle stimulating principle The initial dosage should be 500 I U and is best administered once a week in order to minimize the possibility of antihor mone formation Therapy should be discontinued after three months and if ineffective may be resumed in another three months with a dosage of 1000 I U

Since hypothyroidism is said to affect spermatogenesis adversely the administration of thyroid substance to patients having a lowered basal metabolic rate may be helpful The correction of obesity, malnutrition and vitamin deficiencies and the elimination of excessive alcohol consump tion and fatigue are also recommended

Male Climacteric —Werner[318] popularized the term male climacteric which has been challenged by many on the grounds that it is not a physio-logic accompaniment of aging in men as is the true climacteric of women Nevertheless Heller and Myers [67] have amassed a considerable body of evidence in support of its existence In a study of 23 men having charac teristic vasomotor psychic constitutional urinary and sexual symptoms these workers found all to have significant increases in their urinary ex-cretion of gonadotropins usually at the levels ordinarily present in surgical

castrates. Since a rise does not occur in normal men after puberty even in old age, this finding signifies failure of testicular function. Testis biopsy was performed in 8 cases and revealed abnormal Leydig cells in all. The seminiferous tubules also showed a decrease in size and activity in some cases with hyalinization similar to that found in the Klinefelter syndrome.

In a study of 6 patients with the male climacteric, Howard and his group[146] failed to confirm the presence of testicular histologic abnormalities. Leydig cells were present in normal numbers and presented normal cytologic characteristics. Only 1 patient had nervous symptoms and flashes; 3 of the older men had impotence and 3 of the younger men manifested oligospermia. All disclosed high urinary gonadotropin titers. There is no mention as to whether androgen therapy was administered and whether this resulted in improvement. It is not impossible that some of these are early or mild cases (the ages were thirty, thirty-two, thirty-seven, fifty, fifty-five and seventy-five years) as suggested by the paucity of symptoms. It is conceivable that morphologic alterations in the Leydig cells become apparent only when their function is impaired to a sufficient extent to cause withdrawal symptoms.

According to Heller and Myers, treatment with androgen resulted in a specific response with disappearance of the symptoms. No such effect was obtained when matching placebos were used. Furthermore, no benefit was observed when androgen therapy was administered to a group of psychoneurotic men having similar symptoms but normal amounts of urinary gonadotropins.

The menopausal-like symptoms were regarded as being due to androgen deficiency for the following reasons: (a) the association of histologic evidence of testicular deficiency with high gonadotropic titers; (b) the disappearance of symptoms following androgen therapy but not after placebo administration; (c) the appearance of identical symptoms after surgical castration which are also abolished by androgen treatment.

The syndrome is relatively rare, affecting only a small proportion of men living into old age. It may occur as early as the third decade, the youngest patient being twenty-five years of age. The symptoms have a striking resemblance to those of the menopause: hot flashes, sweating, palpitations, paresthesias, nervousness, impaired ability to concentrate, easy fatiguability, insomnia and loss of sexual vigor are the outstanding symptoms. In most cases there is no demonstrable etiologic factor. In some instances the symptoms are due to known causes of testicular failure, such as bilateral orchitis, trauma, the Klinefelter-Reifenstein-Albright syndrome, testicular tumors (rare), castration and operative compromise of testicular blood supply.

It is pertinent at this point to decry the loose application of the term "male climacteric" to men with similar but often unmistakably psychoneurotic symptoms. Sexual impotence, nervousness, dizziness, insomnia, depression and fatigue are complaints which are common to both the male climacteric and the psychoneurotic. Only infrequently, however, are these symptoms due to androgen withdrawal. In the large majority of men with these complaints androgen therapy is of no avail. When facilities for gonadotropin assay are not available or when testicular biopsy is impractic-

able, a valuable differentially diagnostic aid is a therapeutic trial with androgens. It is important first to ascertain that no contraindications to androgen administration exist. Rectal examination should be performed in an effort to exclude the possibility of prostatic malignancy which would be malevolently influenced by androgens. The presence of edema interdicts the use of sex steroids because of their salt retaining effect. Finally the preservation of spermatogenic function may be an important consideration in the case of some individuals. Since continued androgen administration may inhibit spermatogenesis by means of adenohypophyseal suppression it may be contraindicated in certain cases.

The intramuscular administration of 25 mg. of testosterone propionate in oil 3 times a week for two weeks is an adequate therapeutic test. A lack of response practically excludes the diagnosis of male climacteric and identifies the symptoms as psychogenic. On the other hand a beneficial result may be due to the effects of suggestion to which psychoneurotic patients are often susceptible. Where this is suspected the course of treatment should be repeated using plain sesame oil instead. A continued good response will confirm this suspicion.

Effective therapy in men with this syndrome requires a minimum of 10 to 20 mg. of testosterone propionate once or twice a week. The dosage in the individual case must be determined by trial and error. In severe cases, especially where the climacteric symptoms are only one part of the entire clinical picture of eunuchism or eunuchoidism, androgenic therapy must be more intensive; it then results in widespread general improvement. Maintenance therapy is best continued by means of implantation of pellets of testosterone. In the experience of Heller and Myers methyltestosterone in 4 to 6 times the injected dose of testosterone propionate proved inadequate. Larger doses had the disadvantages of being expensive and causing gastrointestinal disturbances.

Panhypopituitarism.—The term panhypopituitarism is applied to conditions exhibiting a deficiency of all the adenohypophyseal tropic factors. As a result the various target-organs normally influenced by the anterior pituitary gland manifest a deficiency of function. Hypogonadism is but one of the several ensuing endocrine disturbances. In addition decreased hypophyseal thyrotropic and adrenocorticotropic activity produce hypothyroidism (pituitary myxedema) and adrenocortical hypofunction simulating Addison's disease. The total clinical picture is modified by whether it begins before or after the completion of puberty. *Prepuberal* panhypopituitarism extending into adult life results in pituitary dwarfism. The short stature is due to the absence of the pituitary growth hormone during the formative years of childhood. Hypogonadism is represented by infantile genitalia, a high pitched voice and sparse or absent hair on the face, body and extremities. Sexual desire and efficiency are diminished or absent. *Postpuberal* panhypopituitarism, often referred to as Simmonds' disease, presents few if any overt clinical manifestations of hypogonadism. There may be a slight decrease in facial and body hirsutes. Sterility and loss of sexual power may be the sole findings referable to gonadal failure.

Regardless of whether pituitary failure begins before or after the completion of normal growth, the urinary excretion of androgens (17-ketosteroids

and estrogens is very low. These substances are formed and excreted in even smaller amounts than they are in patients with primary testicular insufficiency. This is due to associated failure of the adrenal cortex, normally an important source of steroid hormone production. Decreased pituitary function is also revealed by the insulin tolerance test which discloses a characteristic hypoglycemia unresponsiveness.[219] By this is meant a very slow return of the blood sugar to normal after hypoglycemia is induced by the intravenous administration of insulin.

Pituitary gonadotropins are either absent from the urine or excreted in very small amounts. In 14 individuals (including males and females) suffering from this disease, Klinefelter and his associates[93] found the urinary gonadotropin titer to be less than 6.6 mouse uterine units in twenty-four hours.

Histologic examination of testicular tissue obtained by biopsy shows the seminiferous tubules and Leydig cells to be small and immature, of the type ordinarily found in preadolescent testes. After many years immature or involuted tubules may become fibrotic. According to Charny and Meranze,[6] peritubular fibrosis is a finding of considerable diagnostic and prognostic significance. Its presence is said to indicate an acquired long-standing degenerative lesion which is refractory to gonadotropin therapy. It is claimed that its absence in prepuberal secondary hypogonadism augurs a favorable response to treatment with gonadotropins.

Panhypopituitarism is quite rare and may be caused by a number of diseases involving the adenohypophysis directly, by contiguity, or by interruption of hypothalamico-hypophyseal pathways. Craniopharyngioma, usually suprasellar in location, is the most frequent cause in childhood, while a chromophobic adenoma of the anterior pituitary is most commonly encountered in adults. Much more infrequent causes are vascular lesions compromising the nutritive supply of the pituitary, idiopathic atrophy, traumatic destruction and various inflammatory and neoplastic processes. The different etiologic factors have one feature in common: destruction of enough glandular (anterior) pituitary tissue to result in a deficient or absent activity of all its tropic functions.

An illustrative case is that of a nineteen-year-old man with panhypopituitarism due to a large suprasellar craniopharyngioma described as Case 20 by Howard *et al.*[146]

A diagnosis of suprasellar tumor had been made at the age of nine years and the patient had become nearly blind ten years later. There was no sexual maturation except for the development of some sexual hair. He was only 58 inches tall and his span measured 61 inches. The weight was 118 pounds. He had no beard and there was no temporal hair recession. There was moderate axillary and scant pubic hair. The phallus was infantile and the testes only 2 cm. long. The prostate was very small, the breasts flat and the voice high pitched. The insulin tolerance test was normal. Semen was not obtained. The urinary 17-ketosteroids were 11.2 mg. in twenty-four hours but when repeated were found to be 2.1 mg., which is regarded as the more accurate result. The twenty-four hour urinary gonadotropins were less than 6.5 mouse units on one occasion and less than 3 mouse units when repeated. Testicular biopsy showed undifferentiated infantile tubules, slight thickening of the tunica propria and no Leydig cells.

This patient demonstrated a deficiency of pituitary growth and gonadotropic factors occurring prepuberally. Adrenocorticotropic activity was less involved as evidenced by the moderate axillary hair growth. Reduction in thyrotropic activity cannot be evaluated since the basal metabolic rate was not recorded.

An example of hypogonadism due to panhypopituitarism of postpuberal onset is described as Case 24 by the same authors.[116] In this instance the disease was due to an intrasellar pituitary chromophobe adenoma.

A man of seventy five years first noted weakness and decreased body hair at the age of fifty five years. He had previously fathered 8 children. During the following twenty years he progressively developed cold intolerance, impotence, attacks of vomiting, myxedema and finally cardiac failure. He was 64½ inches tall and weighed 137 pounds. He shaved twice a week, had no axillary hair and but scant pubic hair. The penis and testes were small and the prostate could not be palpated. The breasts were flat. X ray examination and visual fields were normal some years before death. The urinary 17 ketosteroids were 3.0 mg in twenty four hours, later falling to 0.9 mg. A low serum sodium, a positive Wilder test and hypoglycemia unresponsiveness were found. The daily urinary excretion of gonadotropins was less than 3 mouse units. Postmortem examination revealed atrophy of the thyroid, adrenals, prostate and testes. Microscopically the testes showed marked interstitial fibrosis and tubular sclerosis, so that only rare tubules containing a few fat-laden Sertoli cells remained. No Leydig cells were seen.

Therapy of hypogonadism due to panhypopituitarism primarily involves treatment of the underlying cause if possible. Ideally the various lacking pituitary tropic fractions should be administered. However these are not as yet commercially available and one can rely only on stimulation therapy with interstitial cell stimulating hormone (chorionic gonadotropin) or substitution treatment with androgens. The therapeutic program is the same as that previously described for eunuchoidism. When it is apparent that treatment must be continued throughout life it is preferable to employ subcutaneously implanted pellets of free testosterone. Six or 8 pellets weighing 75 mg each provides continuous maintenance doses for three to six months. As is true in all instances of hypogonadism having a prepuberal onset, treatment should be instituted at the age of eleven or twelve years, the time when puberty usually gets under way. Although not a substitute for the pituitary growth hormone, a well defined androgenic effect induced by treatment at this time may be expected to increase the height of the individual. The latter will remain a dwarf but will at least be taller than if he were deprived of that component of growth which is associated with the onset of sexual maturity.

It is not anticipated that replacement therapy with androgenic hormone will do more than efface the manifestations of secretory deficiency. Nevertheless isolated case reports[3, 9, 3, 1, 3] indicate that, in addition, spermatogenesis may occasionally result from androgen therapy.

Thyroid substance is also given in dosages regulated by its effect on the basal metabolic rate.

Relative Hypopituitarism. — This term is employed to designate those instances of hypogonadism which are due to a loss of pituitary gonadotropic stimulation. In contrast to the syndrome of panhypopituitarism only the

gonadotropic activity of the adenohypophysis has failed whereas the other tropic functions remain relatively intact In 1941 Fraser and his co-workers[194] were the first to draw attention to this type of male eunuchoidism which is due to partial failure of the adenohypophysis In the majority of cases no etiologic factor can be demonstrated so that the noncommittal expression idiopathic eunuchoidism with low FSH is often used to describe this group of patients[146 194] Heller and Nelson[70] prefer the designation hypogonadotropic eunuchoidism for the same group

Certain rare diseases are responsible for a small percentage of patients with hypogonadism due to relative hypopituitarism An association with obesity characterizes the very rare condition known as Frohlich s syndrome This is produced by hypothalamic disease which secondarily affects the pituitary gonadotropic function A congenital familial disorder the Laurence Moon Biedl syndrome is also characterized by hypogonadism and obesity In addition these patients manifest other congenital anomalies such as retinitis pigmentosa polydactylism and mental deficiency[221] Although the gonadal insufficiency in this group of cases has generally been attributed to a lack of pituitary stimulation Francke[71] has recently suggested that this is not invariably true and that hypogonadism is not always present in this disease He studied 2 women with all the features of this syndrome who had normal amounts of urinary gonadotropins and little if any, hypogonadism In a third case a male urinary gonadotropins were not estimated but the testicular histology strongly suggested that the hypogonadism was due to a *primary* testicular defect probably also congenital in nature

Also included in this category is the sexual infantilism occasionally associated with marked obesity which occurs in Hand-Schuller Christian disease Extensive granulomatous lesions infiltrated with xanthoma cells involve the regions of the pituitary and tuber cinereum as well as the bones The patient usually a child presents the syndrome of diabetes insipidus exophthalmos and roentgen evidence of rounded areas of decalcification in the bones of the skull Survival into adult life is accompanied by failure of genital development

In almost all patients in this category hypogonadism develops prepuberally *so that the adult subject possesses a characteristic eunuchoidal* habitus The voice is high pitched the genitalia underdeveloped and hair development quite sparse In contrast to the hypogonadism due to panhypopituitarism these individuals are usually tall rather than short and present typical eunuchoidal skeletal changes Other manifestations of hypogonadism are the same but evidence of associated failure of the thyroid and adrenal are usually lacking Since axillary and pubic hair growth is regulated partially by adrenocortical function[95] the curtailment of hair development in these regions is not as marked as it is in panhypopituitarism While the urinary excretion of neutral 17 ketosteroids is reduced it does not reach the extremely low or absent levels found when adrenocorticotropic stimulation is also deficient as in panhypopituitarism The basal metabolic rate is usually within normal limits unless there is an associated deficient pituitary thyrotropic activity Patients with this syndrome also differ from those who are eunuchoidal as a result of primary

This patient demonstrated a deficiency of pituitary growth and gonadotropic factors occurring prepuberally. Adrenocorticotropic activity was less involved as evidenced by the moderate axillary hair growth. Reduction in thyrotropic activity cannot be evaluated since the basal metabolic rate was not recorded.

An example of hypogonadism due to panhypopituitarism of postpuberal onset is described as Case 24 by the same authors.[146] In this instance the disease was due to an intrasellar pituitary chromophobe adenoma.

> A man of seventy five years first noted weakness and decreased body hair at the age of fifty five years. He had previously fathered 8 children. During the following twenty years he progressively developed cold intolerance, impotence, attacks of vomiting, myxedema and finally cardiac failure. He was 64½ inches tall and weighed 137 pounds. He shaved twice a week, had no axillary hair and but scant pubic hair. The penis and testes were small and the prostate could not be palpated. The breasts were flat. X ray examination and visual fields were normal some years before death. The urinary 17 ketosteroids were 3.0 mg in twenty four hours later falling to 0.9 mg. A low serum sodium, a positive Wilder test and hypoglycemia unresponsiveness were found. The daily urinary excretion of gonadotropins was less than 3 mouse units. Postmortem examination revealed atrophy of the thyroid, adrenals, prostate and testes. Microscopically the testes showed marked interstitial fibrosis and tubular sclerosis so that only rare tubules containing a few fat-laden Sertoli cells remained. No Leydig cells were seen.

Therapy of hypogonadism due to panhypopituitarism primarily involves treatment of the underlying cause if possible. Ideally, the various lacking pituitary tropic fractions should be administered. However, these are not as yet commercially available and one can rely only on stimulation therapy with interstitial cell stimulating hormone (chorionic gonadotropin) or substitution treatment with androgens. The therapeutic program is the same as that previously described for eunuchoidism. When it is apparent that treatment must be continued throughout life it is preferable to employ subcutaneously implanted pellets of free testosterone. Six or 8 pellets weighing 75 mg each provides continuous maintenance doses for three to six months. As is true in all instances of hypogonadism having a prepuberal onset, treatment should be instituted at the age of eleven or twelve years, the time when puberty usually gets under way. Although not a substitute for the pituitary growth hormone, a well defined androgenic effect induced by treatment at this time may be expected to increase the height of the individual. The latter will remain a dwarf but will at least be taller than if he were deprived of that component of growth which is associated with the onset of sexual maturity.

It is not anticipated that replacement therapy with androgenic hormone will do more than efface the manifestations of secretory deficiency. Nevertheless, isolated case reports[320,313] indicate that in addition spermatogenesis may occasionally result from androgen therapy.

Thyroid substance is also given in dosages regulated by its effect on the basal metabolic rate.

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Certain rare diseases are responsible for a small percentage of patients with hypogonadism due to relative hypopituitarism. An association with obesity characterizes the very rare condition known as Frohlich's syndrome. This is produced by hypothalamic disease which secondarily affects the pituitary gonadotropic function. A congenital familial disorder, the Laurence-Moon-Biedl syndrome, is also characterized by hypogonadism and obesity. In addition these patients manifest other congenital anomalies such as *retinitis pigmentosa, polydactylism and mental deficiency*.[2,3] Although the gonadal insufficiency in this group of cases has generally been attributed to a lack of pituitary stimulation, Francke[271] has recently suggested that this is not invariably true and that hypogonadism is not always present in this disease. He studied 2 women with all the features of this syndrome who had normal amounts of urinary gonadotropins and little if any hypogonadism. In a third case, a male, urinary gonadotropins were not estimated but the testicular histology strongly suggested that the hypogonadism was due to a *primary* testicular defect probably also congenital in nature.

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In almost all patients in this category hypogonadism develops prepuberally so that the adult subject possesses a characteristic eunuchoidal habitus. The voice is high pitched, the genitalia underdeveloped and hair development quite sparse. In contrast to the hypogonadism due to panhypopituitarism these individuals are usually tall rather than short and present typical eunuchoidal skeletal changes. Other manifestations of hypogonadism are the same but evidence of associated failure of the thyroid and adrenal are usually lacking. Since axillary and pubic hair growth is regulated partially by adrenocortical function,[9] the curtailment of hair development in these regions is not as marked as it is in panhypopituitarism. While the urinary excretion of neutral 17 ketosteroids is reduced, it does not reach the extremely low or absent levels found when adrenocorticotropic stimulation is also deficient as in panhypopituitarism. The basal metabolic rate is usually within normal limits unless there is an associated deficient pituitary thyrotropic activity. Patients with this syndrome also differ from those who are eunuchoidal as a result of primary

testicular disease (Klinefelter syndrome, functional castration) in that they do not develop gynecomastia.

The urinary excretion of gonadotropins is very low or absent. The microscopic anatomy of the testes is that of the prepuberal boy.

A patient reported from Albright's laboratory illustrates the characteristic features encountered in this type of eunuchoidism due to idiopathic relative hypopituitarism. He is Case 74 of a study reported by Fraser and associates[194] and Case 7 of a subsequently reported group.[146]

At the age of seventeen years his height was 61½ inches, span 63¼ inches and weight 99 pounds. There was no beard, axillary or pubic hair. The phallus was 2.5 cm. long, the prostate and right testicle were not palpable and the left testis was bean sized. There was no breast enlargement. The voice was high pitched and he had no erections. When he was twenty-one years of age the height was 65 inches and weight 124 pounds. Adult secondary sexual characteristics were present and the testes remained unchanged. Roentgen examination showed a normal sella turcica. The basal metabolic rate was −20 per cent. Semen was not obtained. Urinary 17 ketosteroids averaged 2.8 mg. per day. The twenty four hour urinary content of gonadotropin was less than 6.5 mouse units. Testicular biopsy (left) at the age of twenty one years showed immature tubules and no Leydig cells.

It is of interest that the counterpart of this syndrome has been described in women with primary amenorrhea and an almost complete lack of secondary sexual characteristics.[93] Urinary gonadotropins are virtually absent but there is no other evidence of pituitary failure.

Therapy is designed to supply the testes with the stimulation which is lacking. It consists of a program of gonadotropin administration as previously described for the management of eunuchoidism. Potent ICSH preparations are available commercially and the therapeutic results are good. It must be emphasized, however, that the presence of peritubular fibrosis or hyalinized tubules usually interferes with the capacity of the testes to respond to stimulation therapy. While it is possible to obtain satisfactory stimulation of intrinsic androgen production by means of gonadotropin treatment, spermatogenic function is not restored. Ideally this would require the simultaneous administration of a potent FSH preparation *for its stimulating effect on the germinal epithelium*. To date no such purified active product has been prepared commercially. One cannot afford to overlook certain isolated reports in the literature[30, 31, 3] in which spermatogenesis was apparently induced in men with pituitary eunuchoidism by the administration of testosterone. There is certainly no objection to its empiric use if gonadotropin therapy is unsuccessful.

Hypogonadism Due to Miscellaneous Extra Gonadal Causes.—In addition to specific intrinsic disease or failure of the adenohypophysis as a cause of hypogonadism there are a number of systemic diseases which produce gonadal failure indirectly by their suppressive action on the anterior pituitary. Chronic malnutrition, diabetes mellitus, deficiency states involving vitamins A and B, hyperthyroidism, adrenocortical dysfunction and chronic renal disease may result in temporary or permanent derangement of pituitary function. These factors may occur in childhood as well as in adult life.

Certain other factors may operate during adulthood to produce hypogonadism. The prolonged administration of estrogens (as in the treatment of inoperable prostatic malignancy) results in a reduction of the size of the testes (due to marked degeneration of the seminiferous epithelium and disappearance of the Leydig cells), suppression of libido and a disappearance of ejaculation.[6,146,2-4] Continued overdosage with testosterone propionate also inhibits spermatogenic function[42,43,44] although, of course, no outward manifestations of gonadal insufficiency appear. Oligospermia has also been reported following the oral use of large doses of methyltestosterone.[3,5] Complete azoospermia resulted from the daily administration of 200 mg. The effects of pituitary suppression are more evident in animals where Leydig cell degeneration can be induced by this means.[40,41]

Much the same group of influences account for the testicular atrophy and gonadal hypofunction observed in some cases of hepatic cirrhosis and acute hepatitis. The mechanism in these instances is believed to involve a disturbance in liver function whereby circulating estrogens are made quitely inactivated and conjugated.[5,9,10] The resulting increase in available estrogens has the same effect as that obtained by their exogenous administration, *i.e.*, inhibition of pituitary gonadotropic activity. However, the co-existence of undernutrition and vitamin deficiency, especially of vitamin B, in these cases suggests that excessive estrogen may not be the only factor involved. Furthermore, there is a possibility of some constitutional defect which predisposes the testes to undergo atrophy when certain individuals are afflicted with cirrhosis.

Testicular atrophy and depressed gonadal function, often associated with gynecomastia, were frequently encountered during and after World War II in prisoners who had been subjected to prolonged starvation.[49,226,3,7] Temporary derangement of hepatic function (with incomplete inactivation of circulating estrogens) was probably the principal mechanism involved. However, it is not possible to exclude a direct suppressive effect of malnutrition upon pituitary activity with secondary depression of testicular function.

Hypogonadism Presumably Due to Genetic Causes.—As mentioned previously, the causative factors in a given case of eunuchoidism are frequently not ascertainable despite exhaustive clinical and laboratory investigation. In such instances it has been pointed out that testicular biopsy and urinary gonadotropin assays are nevertheless of considerable assistance in the evaluation of prognosis and therapy.

From an etiologic standpoint it is important to recognize the fact that the gonads, as well as other organs and tissues, may be the site of primordial or germ plasm defects. The probability of a constitutional gonadal deficiency in certain cases of the Klinefelter syndrome has already been mentioned.[9] Attention has recently been drawn to the likelihood of a congenital testicular defect in some patients with the Laurence-Moon-Biedl syndrome.[71] In connection with the histopathology of the testis in cases of male infertility, reference was made to the occasional occurrence of germinal aplasia of the seminiferous tubules.[312] Engle[314] suggested that in certain instances the absence of tubular germinal epithelium may be morphologically analogous to similar situations encountered in women whose ovarian Graafian follicles show poor or absent development.[90,296]

In the female the gonadal lesion is recognized to be due to a primary congenital defect and is invariably associated with one or more congenital defects elsewhere in the body. These characteristically consist of webbing of the neck (pterygium colli), increased carrying angle at the elbow (cubitus valgus) and shortness of stature which is not true dwarfism but is rather explained on a basis of a primordial defect in bone growth. Various other congenital abnormalities may be found. These include coarctation of the aorta, disorders of the extra-ocular muscles, spina bifida, polydactyly and a number of other evidences of a defective soma. Because of the rudimentary or agenetic ovaries a marked ovarian hormonal insufficiency becomes apparent at the age of puberty. The uterus, vagina and external genitalia fail to develop, the breasts remain infantile and there is only sparse growth of the axillary and pubic hair.

Since Turner[358] first described a group of patients displaying sexual infantilism, webbed neck and cubitus valgus, this category has come to be known as *Turner's syndrome*. It remained for other workers[34-36] to demonstrate the presence of increased amounts of urinary gonadotropins in these patients, thus establishing a primary gonadal insufficiency. The constant presence of associated congenital abnormalities is consistent with the finding of genetically defective ovaries.

With the clinical picture of Turner's syndrome in mind a few investigators have described cases of hypogonadism which they regard as the male counterpart of this disease. Four such cases have been reported to date, each with testicular hypoplasia and webbing of the neck.[169, 379, 330, 331]

The first case of Turner's syndrome in a male was reported by Flavell.[379]

A twenty-one year old man presented extreme webbing of the neck for which he sought and obtained surgical relief. He also had cubitus valgus, claw feet and a cervical spina bifida occulta. Facial hair growth was subnormal and required shaving every third day. Chest hair was absent, axillary hair was sparse and the pubic hair was of the female type of distribution. The phallus was of average proportions while the testes were reduced to one third normal size. The patient was married and claimed to have normal erections and emissions. Hormonal assays and testis biopsy were not performed.

McCullagh's[169] patient was a twenty-one year old eunuchoid who was not quite as typical as Flavell's case but nevertheless also suggests that a condition similar to Turner's syndrome exists in men.

This twenty-one year old man had moderately severe eunuchoidism with a high pitched voice and small testes. Many congenital abnormalities were present including webbing of the neck, cubitus valgus, microphthalmos and right facial palsy. The urinary excretion of 17 ketosteroids was slightly reduced while that of gonadotropin was between 6 and 53 mouse units, apparently not increased. Testicular biopsy showed hypoplasia, thickening of the basement membrane, moderate fibrosis and no Leydig cells; gametogenic elements were distinctly immature.

Greenblatt and Nieburgs[330] reported a less typical case, that of a colored man aged thirty years with azoospermia due to testicular tubular hypoplasia. Leydig cells were present. The gonadotropic content of the serum was not increased. Webbing of the neck and cubitus valgus were present.

Curiously enough, the phallus was larger than normal; the suggestion was offered that this might represent an additional congenital abnormality.

A recently reported case[311] is the least typical and it is questionable whether it should be regarded as an example of Turner's syndrome in the male.

> A ten year old boy, who was only 43 inches tall, showed webbing of the neck, cubitus valgus and bilateral epicanthus. Roentgen examination revealed osteoporosis of the dorsal vertebrae and iliac bones. There was also delayed closure of the epiphyses of the long bones. Testis biopsy disclosed marked changes from the appearance usually noted at this age. The authors point out the similarity of the histologic structure to that encountered in pituitary dwarfism. Furthermore, the urinary gonadotropins were very low even when the patient reached the age of thirteen years. The associated congenital abnormalities were regarded as the dominant reasons for regarding this patient as having a congenital testicular disorder.

That defective gonadal embryogenesis may be responsible for significant testicular deficiency is strongly suggested by the clinical features of a patient studied in our Endocrine Clinic. In this instance there was a complete absence of germinal epithelium in the seminiferous tubules, a condition which has been described by Engle[312] and others[147] as germinal aplasia. The absence of anamnestic and clinico-pathologic evidence of inflammatory or degenerative disease points to a primary developmental defect as the etiologic factor. It has been suggested that germinal aplasia or agenesis is due to a failure of migration of primordial germinal cells into the epithelial mass of the embryonal urogenital ridge.[147,312,314] Germinal aplasia is usually encountered in apparently normal men whose only complaint is infertility due to azoöspermia. The testes may be normal in size[312,314] or small.[146,147] On the other hand, the patient to be described manifests distinct evidence of androgen deficiency with an increased urinary content of gonadotropins. Moreover, the presence of associated congenital abnormalities supports the concept that the testicular defect is likewise genetic in origin. In a broad sense, therefore, this patient qualifies as an example of Turner's syndrome in the male.

> The patient is a thirty-six year old man with markedly reduced libido. He recalled an ejaculation at about the age of twenty-four years and has had no erections since that time. Previously, there were feeble and infrequent erections. He was somewhat short, measuring 63½ inches in height, and slightly obese, weighing 160 pounds. The arm span was 63¾ inches. The voice was masculine in pitch. The cranial hair was abundant and fine in texture. The facial hair was reduced in amount so that shaving was required but twice a week. Axillary hair was normal while the pubic hair presented a feminine type of escutcheon. The hair on the chest was almost absent. Both breasts were enlarged and firm. The distribution of fat over the hips and buttocks was of the female type. Psychologically, he was infantile and functioning on a moronic level. The penis was subnormal in size and the testes were very small and soft, measuring 1.5 cm. in their longest diameter. The prostate was moderated in size. Roentgen examination showed normal development of the long bone. The epiphyses were closed and there was no osteoporosis. The sella turcica was of normal size. Multiple congenital anomalies of the cervical vertebrae were present. There was a reversal of the lordotic curve normally seen in this region. This was apparently due to atlanto-occipital fusion and partial fusion of the spinous processes and posterior articulations of the second

and third cervical vertebræ. Bilateral cervical ribs were present. Moderate hypertrophic changes were noted about the bodies of the fifth, sixth and seventh cervical vertebræ with narrowing of the interspace between the latter two. The neck was rather short and thick but not webbed. A large firm mass had been present in the right lobe of the thyroid gland for many years. This was composed of an aggregate of smaller nodules which were presumably cysts

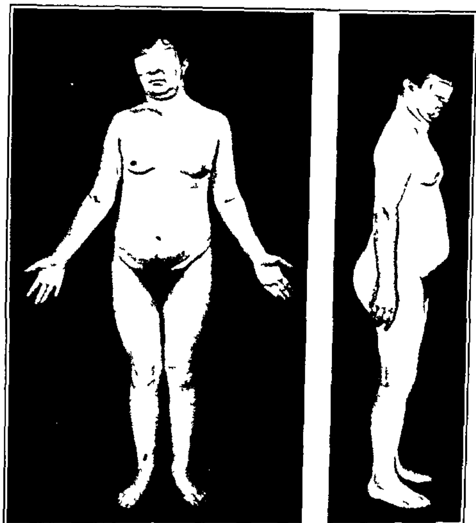


FIG. 43.—Appearance of a 36 year old man with primary eunuchoidism and clinical features suggestive of Turner's syndrome. There is gynecomastia, female type of pubic hair escutcheon, wide hips and buttocks, small penis and testes, short neck and cubitus valgus. The urinary gonadotropins are elevated.

or adenomas. Cubitus valgus was present. Diabetes mellitus was an incidental, previously unrecognized finding. The visual fields were normal. The electroencephalogram and basal metabolic rates were within normal limits. The urinary excretion of neutral 17-ketosteroids was 11.1 mg. per twenty-four hours, which is at the lower range of normal. The assay for urinary gonadotropins showed a marked elevation (positive at 160 m.u.u.). Seminal fluid could not be obtained for analysis because of the absence of ejaculation. Histologic

examination of a segment of testis removed by biopsy showed small seminiferous tubules with slight thickening of the lamina propria. The only cellular elements contained within the tubules were Sertoli cells. Cells of the spermatogenic series could not be definitely identified. A few barely recognizable ghost tubules were present. There was no well defined sclerosis or hyalinization of the tubules. Conspicuous numbers of Leydig cells were present in the interstitial tissue.



FIG 44 —Testicular biopsy from a 36 year old man belonging to the category of Turner's syndrome. The seminiferous tubules are reduced in size and show slight thickening of the lamina propria. The tubules contain only Sertoli cells recognized by their ovoid nuclei and distinct nucleoli. Leydig cells are conspicuous in the intertubular tissue. H & E stain (× 340)

The increased urinary gonadotropins indicate that this patient's hypogonadism is primarily testicular in origin. The absence of tubular sclerosis and hyalinization excludes the possibility of Klinefelter's syndrome. The apparent presence of germinal aplasia suggests a congenital disorder as the causative factor. The associated congenital anomalies (cervical vertebræ, short neck, cubitus valgus and possibly the thyroid lesions and mental deficiency) strengthen the view that the testicular deficiency is but one of several genetic defects present in this patient. He may be regarded therefore as meeting the requirements for inclusion among the group of hypogonadal patients representing the male counterpart of Turner's syndrome.

Despite the apparent rarity of classic Turner's syndrome in the male there is little doubt that analogous genetic defects occur in both sexes. These may involve general body structures as well as the endocrine glands including the gonads. The production of hormonal disturbances depends of course upon whether the secretory function of the involved gland becomes impaired.

Tumors of the Testis —Like the other endocrine glands the testis may be involved by tumor formation. This may be asymptomatic or may give rise to the conventional symptomology of neoplastic disease of non-endocrine organs. In certain instances however tumors of the testis may in addition be associated with alterations in the hormonal status of the

individual. At times these are due to the ability of certain tumors to elaborate hormones, notably gonadotropins and, to a lesser extent, androgens and estrogens. Usually the etiologic mechanism involved in the production of associated endocrinologic disturbances is not clear. It is possible in some cases, that testicular tumors may be the result rather than the cause of a hormonal dysfunction. This is suggested by the high tumor incidence in cryptorchids and in male pseudohermaphrodites. It is also possible that a testicular tumor may disturb the hormonal balance of an individual by causing testicular destruction or other secondary effects on the gonadal tissues. In any event it is not surprising that testicular tumors are occasionally associated with hormonal disturbances in view of the secretory potential of embryonal and postnatal testicular tissue. Interrelationships between the testis, pituitary and adrenal glands probably play a role in the pathogenesis of endocrine disturbances in these patients but there is little or no understanding of the mechanism involved. Most of our current knowledge concerning the endocrinology of testicular tumors stems from chance observations of clinical cases. The scarcity of clinical material and the frequent lack of facilities for complete hormonal study have seriously hampered developments in this direction.

Although extremely interesting from an endocrinologic point of view, it must be emphasized that testicular tumors are quite uncommon, comprising about 1 per cent of tumors in the human male. The incidence of cancer of the testis reaches a peak from the thirty-fifth to the thirty-ninth year and is quite low after the age of sixty years. It is also to be noted that overt abnormalities of the secondary sex characteristics are very rare, although significant deviations in the urinary hormonal pattern are quite common.

Practically all testicular tumors are malignant or potentially so. From the standpoint of pure pathology there is little unanimity regarding their classification and nomenclature. This is primarily due to widely differing interpretations of pathogenesis. The latter have also led to varying opinions concerning the significance of hormonal changes. Most testicular tumors are believed to originate from embryonal testicular cells and the divergent views on their histogenesis vary according to which type of embryonal cell is regarded as the tumor progenitor.

In 1906 Chevassu[307] was the first to describe and distinguish between the two common testicular tumors, teratoma and seminoma. He maintained that the latter was a carcinoma of the seminal epithelium ("epithelioma seminal"). He also described the rarer interstitial cell tumor and the testicular (tubular) adenoma. In 1911 Ewing[3] stated the view that seminomas arise from teratomatous precursors rather than from the seminal epithelium. He drew this conclusion after finding seminoma or seminoma-like tissue in some teratomas. This was explained on the basis of a "one-sided development" of a single cellular type to the exclusion of other teratomatous elements. This unicellular tumor he called "embryonal carcinoma," a designation and interpretation which is still widely accepted. Recently Willis[33] published the results of his studies of 50 testicular tumors examined by serial section. His conclusions differ from those of the Ewing school. In part they re-assert the autonomous origin of seminoma from

seminiferous epithelium In addition he interprets his findings to indicate that chorionepithelioma is not a distinctive type of growth of chorionic origin but is only a form assumed by hemorrhagic necrotic cellular tumors of other kinds usually teratomas

Regardless of varying histogenetic hypotheses and nosologic considerations it is of practical value to recognize certain major types of testicular tumor For the most part these are histologically distinct and are often associated with characteristic endocrine disturbances Nevertheless, it must be emphasized that many tumors contain divergent cell types This often results in differences in classification and interpretation of the same specimen by different, equally competent observers

1 *Seminoma* Synonyms include seminal carcinoma embryonal carcinoma embryonal carcinoma with lymphoid stroma and 'spermatocytoma According to Masson[333] true seminoma (spermatocytoma) can be distinguished from false seminoma by its different cytologic derivation The former is held to originate from the spermatocyte and has no homologue in the ovary The false seminoma is said to arise from undifferentiated embryonal cells is therefore termed gonioma and is *regarded as homologous with the ovarian dysgerminoma*

In general these tumors are composed of fairly uniform cells closely resembling the cells of the seminiferous tubules In a very careful study of serial sections of 21 seminomas, Willis[332] could find no sign of teratomatous elements The concept of submergence and obliteration of pre-existing teratoma by seminomatous growth is accordingly regarded as unsubstantiated In 5 other cases seminoma was found to co-exist with teratoma but *there was no evidence of histogenic relationship between the two tissues* While such co-existence cannot be regarded as fortuitous it has not been satisfactorily explained

Seminoma is the most common type of tumor and occurs most frequently between the ages of thirty and fifty years A single case[334] in a boy of sixteen years is the only reported instance under the age of twenty years These tumors appear about a decade later than teratomas and produce *no overt signs of endocrinologic significance Many grow slowly and* metastasize late so that prompt surgery can effect a permanent cure They are more apt to be radiosensitive than are teratomas Many patients with seminoma excrete increased amounts of gonadotropins in their urine In some cases the increase is due to large amounts of follicle stimulating hormone (FSH) in others there are excessive quantities of chorionic gonadotropin having a biologic action similar to that of interstitial cell stimulating hormone(ICSH)[80,81] The significance of the *different types* of gonadotropins found in these patients is discussed below

The urinary excretion of neutral 17 ketosteroids in patients with seminoma of the testis has been very incompletely studied The only available report is that of Warren[335] who found an average of 20 7 mg per day in 4 men with this disease the individual results were 18 0 32 2 15 4 and 20 0 mg indicating a trend toward a slightly increased excretion

Hamburger and Godtfredsen[336] determined the urinary content of biologically active androgens in 19 men with seminoma Subnormal values were found in 15 and the average for the 19 patients was about one fifth

that of normal men in a corresponding age group. They attributed the low output to destruction or removal of the affected testis.

Estrogen excretion in the urine was also studied by Hamburger.[80] Biologically active estrogens were present in normal amounts in nine out of 10 men with seminoma; in the remaining case there was a slight increase.

From the foregoing observations it appears that patients with testicular seminoma often excrete increased amounts of gonadotropins and subnormal quantities of androgens in their urine. The urinary content of estrogens tends to remain within normal limits while that of 17-ketosteroids may show a slight increase.

2. *Teratoma.*—This is a heterogeneous tumor containing a variety of tissues *foreign to the testis. It is the counterpart of the ovarian teratoma*, both originating from embryonal totipotent cells. A sharp contrast exists between the two sexes in that testicular teratoma is almost always malignant, whereas in the ovary most teratomas are of the benign "dermoid cyst" type. While Ewing[12] held that most testicular tumors, including seminoma, *are fundamentally of this type, it is Willis'*[23] *contention that embryonic* epithelial growth in teratomas has been mistaken for seminoma, the latter having an entirely independent origin.

Because of its mixed nature and multiple germ cell layer derivation, several varieties of teratomatous lesions have been described. These include embryonal carcinoma, embryonal adenocarcinoma, mixed epithelioma, and adult teratoma. Adult teratomas are extremely rare, being composed of mature tissues such as bone, muscle, *etc.*; they appear histologically benign but are potentially malignant. The mean age of patients with teratomas is about ten years younger than that of patients with seminomas. Of great importance is the fact that teratoma, unlike seminoma, may occur in childhood. As a rule these tumors have a graver prognosis than do seminomas. They are actively invasive, metastasize early and are usually resistant to radiotherapy. As with seminoma, patients with teratoma display no outward endocrine signs (except for the gynecomastia of chorionepithelioma). However, excessive quantities of urinary gonadotropins are often found. The chorionic (ICSH) type is more commonly present than the FSH type but frequent exceptions exist.

Meager reports indicate that patients with testicular teratoma excrete increased amounts of neutral 17-ketosteroids. Warren[375] found the daily output to be 28.6 mg. in 1 patient. In 2 other patients Dorfman and Shipley[337] found an average excretion of 22.8 mg. in twenty-four hours.

The urinary excretion of androgenically active material is often reduced in men with teratoma of the testis. According to Hamburger and Godtfredsen[336] this finding is neither as frequent nor as marked as it is in cases of seminoma. Of 12 patients with the chorionic type of gonadotropin in their urine, half had a normal androgen excretion. Where androgens were reduced they were still present in twice the amount found in the seminoma patients. Hamburger is of the opinion that the formation of large quantities of chorionic gonadotropin may stimulate the other testis to produce androgens which would tend to compensate for the decreased output by the diseased testis.

The excretion of estrogens in the urine of patients with teratoma of the testis tends to be increased especially when large amounts of chorionic gonadotropin are being formed. Hamburger[3] pointed out a direct correlation between the two, the three highest estrogenic titers being found in urines containing more than 100,000 mouse units of chorionic gonadotropin per day. These were patients with lesions described as mixed epithelioma frequently containing syncytial or trophoblastic tissue of the type usually termed chorionepithelioma.

3 *Chorionepithelioma*.—Much less frequent than the ordinary seminoma and teratoma and occasionally found in conjunction with them, this tumor is derived from pluripotential undifferentiated primordial epithelial cells. It is in effect a rapidly growing teratoma, grossly hemorrhagic and necrotic. Irregular clumps of polyhedral cells and fused syncytial masses are found on microscopic examination of the better preserved areas. Not only does the pathologic anatomy of this tumor resemble that of its placental-derived counterpart in the female but it has a remarkably similar hormonal activity. Such large quantities of chorionic gonadotropin are secreted by the tumor and excreted in the urine that a positive pregnancy test (Aschheim-Zondek or Friedman test) is often obtained.

Data concerning the urinary hormonal pattern (apart from chorionic gonadotropin) is very limited due primarily to the rarity of the disease. The urinary excretion of neutral 17-ketosteroids was reported by Twombly[61] to be 24 mg in a man with widespread chorionepithelioma arising from the testis. This is regarded as a high normal value. It is a matter of parenthetical interest that a normal urinary excretion of 17-ketosteroids was found in two women with chorionepithelioma.[337] By way of contrast Twombly reported a low urinary excretion of androgens in the same patient whose 17-ketosteroids were at a high normal level.

Patients with testicular chorionepithelioma are apt to excrete increased amounts of estrogenic material in their urine. This is not observed as frequently as is the increased excretion of chorionic gonadotropin. As previously mentioned in connection with teratoma, which is pathogenetically identical with chorionepithelioma, the quantity of estrogen excreted may vary directly with the amount of chorionic gonadotropin.[60] Twombly's case cited above revealed a markedly increased urinary excretion of estrogens. However, the Smiths[338] found low urinary estrin levels in 4 cases of chorionepithelioma, 3 in men and 1 in a woman. The discrepancy in these findings remains unexplained. It is probably related in part to underlying differences in the secretory capacity of differently composed teratomatous tumors.

Free pregnanediol was excreted in significant amounts by a man with testicular chorionepithelioma cited by Twombly.[61] This is the same patient who excreted large quantities of gonadotropin, high normal amounts of 17-ketosteroids, subnormal amounts of androgens and greatly increased levels of estrogens. These findings indicate that under certain circumstances progesterone or its metabolic product, pregnanediol, may be formed. It is to be regretted that no other studies concerning this important hormonal observation are available.

Gynecomastia is occasionally observed with testicular chorionepithelioma and has been accompanied by secretory activity in the breasts in

certain cases The increased excretion of estrogens demonstrated in some patients suggests that breast enlargement may be an effect of estrogenic stimulation It is apparent from the meager studies at hand that this cannot always be true and that the precise mechanisms involved in the production of gynecomastia are in need of clarification

Chorionepithelioma of the testis is a highly malignant tumor which is rapidly invasive Metastases may occur from a relatively small primary tumor and these may produce the first symptoms which call attention to the disease

4 *Leydig Cell Tumor* —Neoplasms of the interstitial cells of the testis are very rare A comprehensive review of the cases reported before 1937 with a detailed and critical discussion of the pathologic findings was presented by Jemerin[366] Although Friedman and Moore[339] found Leydig cell tumors in 1 per cent of 922 pathologic specimens of testicular tumors, only 40 cases have been recorded in the literature by the end of 1949[371,372] Of these 29 have been in adults and 11 in children It is probable that several cases have been encountered but not reported A general idea as to the relative incidence of malignancy of these lesions is obtained from the studies of Nation Edmondson and Hammack[340] In an analysis of 26 acceptable cases these workers found 21 to be benign and 5 malignant Malignant tumors have been observed only in adults

Available data indicate that these tumors may occur at any age from childhood to senility although the peak of their incidence usually coincides with the era of sexual activity They vary in size but are characteristically small In several instances they escaped recognition by the patient In some cases even the physician could not be certain of the existence of a tumor in the testicle In this event reliance must be placed on the consistency of the testis as compared to that of its contralateral mate Transillumination may be of value in detecting the presence of a clinically impalpable small tumor mass The latter, however, may not be found until serial often microscopic sections are examined The color of the tumor may vary but is usually of a yellow or brown hue due to the presence of large amounts of lipoid and pigment It is usually encapsulated although in some cases there is merely a rim of compressed uninvolved testicular tissue rather than a true capsule

Microscopically the dominant tumor cytology is usually that of Leydig cells which are completely normal in appearance except for being present in huge numbers Less commonly the tumor cells are not completely normal Leydig cells but are sufficiently similar to establish their true nature Much of the difficulty in accepting reported cases as legitimate instances of interstitial cell tumors stems from the lack of a clear differentiation from Leydig cell hyperplasia Warren and Olshausen[341] point out that too little is known of the normal variations of interstitial cells and that a distinction between hyperplasia and neoplasia is often difficult In a study of 12 reported cases of true hyperplasia of the interstitial cells of the testis (including two of their own) they found the majority to occur after the age of forty five years in small atrophic testes True uncomplicated hyperplasia is extremely rare and is usually discovered at postmortem examination The hyperplasia of Leydig cells frequently encountered in chronic

diseases, cryptorchidism, environmental changes and after exposure to radioactive agents is often more apparent than real and may be due entirely or largely to diminished spermatogenesis. In many instances where the seminiferous tubules are hyalinized (as in the Klinefelter syndrome) clumping of Leydig cells is frequently noted. At times this may reach such marked proportions as to simulate adenoma formation. Furthermore there are no definite criteria for malignancy except that of metastasis. The presence of Leydig cells in the tunica albuginea or even in the structures of the spermatic cord is not regarded as evidence of invasion but rather as instances of ectopy. Even the absence of metastases over a prolonged period of time does not assist in establishing the possible benign nature of the testicular lesion in a given case. One of Masson's[342] patients enjoyed good health for nine years after orchidectomy, then to succumb to generalized dissemination of the disease. The presence or absence of cellular mitosis assists neither in the differentiation between hyperplasia and neoplasia nor in the distinction between benign and malignant tumors. Cellular division was amitotic in both of Masson's patients with malignant Leydig cell tumors.[342,343]

Clinical manifestations of an endocrine type were present in one third of the reported cases of Leydig cell tumor.[340] The majority of these were boys with precocious sexual and somatic development. It is important to emphasize that this is a *pseudosexual* precocity since spermatogenesis is absent. The effects of excessive androgen secretion are quite naturally more apparent in childhood than in adult life when the subject has already been subjected to normal physiologic androgenic stimulation. Recognizable endocrine disturbances in the adult consists only of gynecomastia, which has been reported in 3 cases[340,344,345] out of 29 men with Leydig cell tumors. Regression in the size of the breasts occurred in 2[344,345] after orchidectomy. No satisfactory explanation has been offered concerning the etiology of breast enlargement in this disease. A stimulating effect of androgens on breast structures has been demonstrated in the experimental animal[229,230,231] and in human male hypogonadism.[228] Efforts to relate these observations to the problem at hand are purely speculative.

Excluding disturbances in the urinary hormonal pattern (which often have *no representation in the clinical appearance of the patient*) overt clinical stigmata of an endocrine disorder are much more frequent in this disease than in other types of testicular tumor. This is to be expected from the excessive quantity of androgenic hormone produced.

The endocrine effects of Leydig cell tumors are best studied in the afflicted child. Eleven cases in children have been reported in the literature[65,346,347,348,349,350,371,372] and it is important to realize that all 11 presented definite evidence *of premature androgenic stimulation characterized by the precocious appearance of puberty*. In some, precocious somatic development was also present. The tumor was benign in every case and was accompanied by gynecomastia in 1 instance.[350] In all cases developmental changes were first noted about the fifth year of life. After orchidectomy regression of sexual precocity occurred completely in 2, partially in 3 and not at all in the remaining cases.

The first patient recorded in the literature was that of Sacchi[316] who according to Stewart, Bell and Roehlke[318] misinterpreted the pathologic lesion as a teratoma. The findings in this case are worthy of summary.



Fig. 45.—Sacchi's[316] case of Leydig cell tumor of the testis in a 9½ year old boy. The sexual and physical development is that of an able bodied young man. Details are described in the text. This photograph was taken 15 days after removal of the tumor.

The boy showed no abnormalities until he was five and a half years old when the phenomena of puberty began to appear. Rapid growth of the skeleton and muscles appeared, axillary, facial and body hair developed and the voice became deep. The left testis became larger than the right. When examined at the age of nine and a half years he had the appearance of a young man showing excessive skeletal and muscular development. He was 57 inches tall and weighed 98 pounds. The hair of the beard was 2 inches in length; the length and circumference of the phallus each measured 3.6 inches. Libido was present with frequent erections although there were no ejaculations. The left testis was enormously enlarged and was estimated to measure 10 cm. in its greatest

diameter while the right was 1 cm in diameter Mental development was not precocious The left testicle was removed and found to contain a tumor weighing 289 grams and measuring 12 × 10 cm One month later the hair on the limbs and bearded region of the face disappeared and the pitch of the voice became high again Three months later the moustache was still present but hair was scarce on other parts of the body Libido was no longer present The penis was now 3 inches long and the right testis had grown larger Ten months postoperatively no further change was noted There was no regression of the skeletal or muscular development

The patient reported by Werner and his associates[35] presented the typical picture of precocious sexual and somatic puberty most often encountered in children with this disease Although the authors could not definitely exclude the possibility that the tumor originated from ectopic adrenal cortical tissue the virilizing effects on the subject are nevertheless identical and characteristic

At the age of five and one-half years abnormal hair growth was first noted about the external genitals which were larger than normal The latter continued to increase in size and frequent erections were noted Hair growth soon appeared in the axillæ and on the face lips and chin When examined at the age of six years and nine months he was at least 6 inches taller than average *normal boys of his age and about 20 pounds overweight His muscles were* firm and overdeveloped and the facial features were of the late adolescent type The voice had become deeper and had increased volume He had a heavy growth of coarse scalp hair and marked hair growth about the scrotum and pubis The prostate was moderately developed the penis measured 3.75 inches in the flaccid state and was 1.5 inches in diameter The left testis was 1 cm long and 8 mm in diameter the right was the size of a medium sized olive and both were firmer than normal It was stated that the boy sought the company of adults rather than his own contemporaries Roentgen examination revealed a markedly advanced degree of bone development The Friedman test for chorionic gonadotropin in the urine was negative No other hormonal assays were performed Although a definite tumor was not palpated the right testis was suspected of harboring a neoplasm and orchidectomy was accordingly performed A tumor was found and the histologic examination was reported to be similar to that found in another case of Leydig cell tumor in a boy[35] Three and one half months after operation the facies had become more child like the coarse hair on the upper lip had disappeared and there was less genital hair growth His formerly aggressive attitude was now reported by his mother to have given way to gentleness The voice and penile state remained unchanged

Another illustrative case is that reported by Rowlands and Nicholson[347]

Nothing abnormal was noted in this boy until the age of six years when he began to grow rapidly At seven years of age his voice became low pitched and at eight he showed signs of puberty When examined at the age of nine years his appearance was that of a fully grown young man He was 5 feet tall and measured 34 inches around the chest He was powerfully built and vigorous There was considerable hair development on the chest loins and pubis The penis was fully developed The right testis was normal while the left was about 5 times as large The boy's intelligence was found to be above average and he displayed normal behavior He avoided girls and there were no indications of libido The testicular mass was extirpated and the testis was found to be uniformly replaced by an interstitial cell tumor Re-examination two years after operation showed no regression of the signs of puberty and he was shaving regularly However he had grown only ¾ of an inch during this time (Fig 46)

Reports of hormone assays in patients with Leydig cell tumors are very meager. Urinary gonadotropin and estrogen have been quantitated in only 1 case, that of Masson;[342] they were 110 and 113 mouse units respectively and regarded as slightly elevated. The urinary excretion of 17-ketosteroids was determined in the same patient by Venning[351] and found to be 1040, 1035 and 980 mg. per day. The serum 17-ketosteroids were elevated to 16 mg. per cent. Masson[342] has remarked that the urinary 17-ketosteroids



Fig. 46.—Appearance of a 9 year old boy with a Leydig cell tumor of the testis reported by Rowland and Nicholson.[347] He is 5 feet tall and looks like a young man of about 18 years. The muscles are well developed and there is abundant hair on the chest. A normal boy of the same age is included for comparison.

should have been even higher in view of the widespread and extensive metastases in this case. The liver which was riddled with disseminated tumor weighed over 3000 grams. After hydrolysis the conjugated 17-ketosteroid (sodium androsterone sulphate) which was only weakly androgenic was found to yield androsterone and androstenone-17[353] which are biologically androgenic.

Assays of whole urine for the presence of increased amounts of chorionic gonadotropin (Friedman or Aschheim-Zondek test) have been done in 4 cases. They were negative in 3[85, 348, 350] and positive in 1, the patient of

Hunt and Budd[345] It is difficult to understand why an interstitial cell tumor should elaborate chorionic gonadotropin This raises a question as to the validity of the pathologic diagnosis in this case The issue is not clarified by a previous brief report of the same case[344] in which it was stated that assay of the urine prior to operation and of the tumor after operation was negative for prolan

The chemical and laboratory data in patients with Leydig cell tumors lend additional support to the probability that the normal androgenic hormone is elaborated by the interstitial cell of Leydig It is of interest that while these tumors produce hypergenitalism and precocious physical development in boys the endocrine findings in adults suggest a reverse effect The occurrence of gynecomastia aspermatogenesis atrophy of the uninvolved testis sexual impotence and sterility in some men with this disease have been regarded by some workers as being due to feminizing effects However the possibility of pituitary suppression by excessive androgen production cannot be dismissed in these instances One can only speculate on the role of estrogens in the production and symptomatology of the disease Estrus-producing substances (natural or synthetic) have long been known to cause Leydig cell tumors in certain (Strong A) strains of mice[26 27 124] On the other hand the administration of effective doses of estrogens for as long as nine months to the human male with prostatic carcinoma was found by Nelson[25] to cause a complete disappearance of Leydig cells with no evidence of new cell formation From the meager data available no conclusions can be drawn concerning the etiology of these tumors By the same token there is no clear explanation for the endocrine effects occasionally observed in the adult with this disease

Evidence of potent protein and electrolyte anabolic effects of excessive androgen production is apparent in some adults with this disease as well as in children The clinical paradox of well preserved nutrition and muscle strength in patients near death from widespread dissemination of malignant interstitial cell tumor is worth remembering It was demonstrated in both of Masson's patients[342 343]

5 *Sertoli cell tumor and tubular adenoma* —These are rare tumors of the testis which were first described by Pick[357] as adenoma tubulare testiculare ovarii He found them in ectopic testes and later[358] in the ovotestis of a true hermaphrodite Details of the microscopic anatomy have also been set forth by Masson[306] Kruckmann[359] in 1937 reported 1 case of his own and collected 20 cases from the literature Of the 21 cases 14 were in patients with ectopic testes Seven of these were male pseudohermaphrodites In 7 additional cases the tumors occurred in ovaries Three of these patients had menstrual disorders while the remaining 4 showed evidences of masculinization which partially regressed in 2 after removal of the tumor

These tumors arise from the non-spermatogenic component of the seminiferous epithelium, i.e. the Sertoli cells They occur chiefly as small multiple benign tumors in cryptorchidism and male pseudohermaphroditism As stated above histologically indistinguishable tumors are also found in the ovary although their histogenesis in the female gonad is not clear According to Teilum[56] these tumors originate in either sex gland from a primordial male-directed testicular blastema retained from the undif

ferentiated embryonal gonad. Such vestigial rests may develop into Sertoli cell tumors (tubular adenoma of Pick) of the testis or tubular adenoma of the ovary. On the other hand the same vestigial remnants of primitive germ cells may differentiate into Leydig cell tumors of the testis or homologous tumors of the ovary. The latter in Teilum's opinion include arrhenoblastoma, adrenal rest tumors and luteomas.

Sertoli cell tumors are much more common in the dog where they may cause feminization.[150,360,361] There is considerable evidence to suggest that these tumors in the dog are homologous with human Sertoli cell tumors and tubular adenomas. However, manifestations of a hormonal influence in the human cases is usually lacking. Nevertheless, congenital abnormalities of the reproductive system (cryptorchidism and pseudohermaphroditism) are usually associated. It is not known whether the latter are due to an endocrine disturbance.

The literature contains only 1 report of a Sertoli cell tumor in an otherwise normal man with descended testes. In this case, reported by Teilum,[24] feminizing effects were produced by the tumor. These were attributed to estrogen elaboration by the Sertoli cells, a phenomenon also observed in dogs with similar tumors. Because this case is so unique it is herewith presented.

> The patient was a fifty-three year old married man with a twenty-three year old son. Enlargement of the left testicle had been present for thirty years; further increase in size had occurred in the previous few years. Medical advice was sought because of breast enlargement which had appeared within the past year. In addition sexual impotence had been present for three years. There had been no weight loss. Bilateral gynecomastia was evident but there was no secretion from the nipple. Chest hair was absent but the distribution of the pubic hair was of the male type. The left testis was the size of a goose egg and was firm, smooth and freely movable; it did not transilluminate. The right testis was the size of a pigeon egg and felt soft and atrophic. The penis was normal. Left orchidectomy was performed. On section a tumor measuring 6 × 4 × 3 cm occupied the entire gland except for a 4 to 5 mm wide rim of apparently normal testis tissue in one section. Microscopically this was found to be composed of atrophic, partly hyalinized tubules. A well-defined connective tissue capsule was present around the tumor. The cut surface was intensely yellow in color resembling lutein tissue. Within two months after operation the gynecomastia had regressed greatly although it was still evident six months later.

The histologic appearance of the tumor in this case is said by Teilum to be identical with that of ovarian arrhenoblastoma. Although morphologically homologous, the testicular tumor is feminizing in its effects while its counterpart in the ovary is masculinizing. This is attributed by Teilum to estrogen producing tumorous Sertoli cells in the former and androgen producing precursors of Leydig cells in the latter. Unfortunately, hormone assays were not performed prior to operation in this case so that this hypothesis cannot be substantiated.

Teilum's concept of morphologic and functional homology between certain ovarian and testicular tumors based on a common blastemic origin is orderly and appealing. It attempts to explain certain obscure clinicopathologic findings. However, it has not been generally accepted because of insufficient confirmation.

The equally rare epithelial tumors of the *excretory ducts* of the testis are probably pathogenetically identical with Sertoli cell tumors. Those that occur within the testis arise from the straight or rete tubules in which the epithelial cells are really modified Sertoli cells. In view of the fact that the non-spermatogenic epithelium of *the convoluted tubules is histogenetically* allied to that of the excretory tubules, it is reasonable to group their respective tumors together.[332] Three tumors are described by Willis[332] who interprets them to be carcinomas of the intratesticular excretory duct system. The clinical data furnished with these cases are insufficient for evaluation of endocrine effects. Attention is drawn to the fact that ductal tumors of the testis are malignant while tubular adenomas (said to be derived from the same epithelial element) are *multiple and benign*. The Sertoli cell tumor described above was also apparently benign.

The Endocrine Aspects of Testicular Tumors.—From the foregoing discussion it is apparent that hormonal disturbances frequently accompany tumors of the testis. The mechanisms underlying these alterations in the hormonal status of the patient are often not clear. It is to be hoped that more complete studies, especially with the aid of newer methods of endocrine investigation, will lead to more precise knowledge of the etiology and abnormal physiology of these tumors.

Hormones as a cause of testicular tumor.—The hormonal relationships of testicular tumors have been comprehensively discussed by Twombly.[81, 362] Considerable evidence from experimental sources and clinical material suggests that endocrine factors may be of contributory significance in the etiology of testicular tumors. For example, teratoma of the testis can be produced in the fowl by intra-testicular injections of zinc or copper salts. However, this occurs only when the animal's own hormones are active (as in the spring) or when stimulated by injected anterior pituitary hormone.[363] The administration of hormones alone is ineffective, indicating that their role in the formation of these tumors is secondary. The prolonged administration of natural and synthetic estrogens to the Strong A and related strains of mice has been shown to produce Leydig cell tumors.[36, 37, 134] These are androgenically active, malignant and metastasize widely. This phenomenon appears to be genetically conditioned since it is highly restricted to a specific strain of one species of animal.

Certain observations in the human also suggest that hormonal influences may play a role in the formation of certain testicular tumors. In a survey of over 7000 recorded cases of testicular malignancy, Gilbert and Hamilton[298] found unilateral or bilateral cryptorchidism in 11 per cent. This incidence of cryptorchidism is about 50 times that encountered in a large section of our adult male population, the latter being 0.23 per cent according to Army statistics.[364] In Twombly's series of 203 cases of teratoma testis 13.3 per cent were associated with cryptorchidism.[81] Trauma to the superficially situated inguinal testis and abnormal environmental temperatures in the case of the abdominal testis have been thought to play a part in the frequency with which ectopic testes become malignant. That this cannot always *be true is evident from the fact that a tumor occasionally* is found in the descended testis rather than in the undescended one. Furthermore, tumor formation has been reported to occur some time after an undescended

testicle has been successfully brought down into the scrotum surgically[307,308] or by hormone administration.[334] Gilbert and Hamilton[298] stress the point that *carcinoma is not necessarily due to testicular ectopy.* The tendency to tumor formation is correlated to a greater degree with associated congenital abnormalities. Ectopic testis itself may be of congenital origin *and congenital inguinal hernia is a frequent associated finding.* Finally pseudohermaphroditism is not infrequently present. Although its cause is not known, male pseudohermaphroditism is a congenital disorder and was found in 11 per cent of 340 intra-abdominal testes involved by malignant tumor.[298] Since some cases of cryptorchidism and pseudohermaphroditism may be due to a congenital endocrine dysfunction, the possibility of a hormonal factor in the production of tumors of these gonads is again raised.

The incidence range *of testicular cancer is primarily from puberty to the fifth decade of life.* The disease is rare in childhood and after the sixtieth year and reaches a peak from the thirty-fifth to the thirty-ninth year of life.[98] *This corresponds to the individual's period of sexual activity* and once more suggests a relationship between hormones and these tumors.

Finally, certain unexplained hormonal findings in men with testicular tumors point to the possibility of an etiologic endocrine factor. Hamburger and Coldtfredsen[336] showed that 75 per cent of patients with testicular seminoma excreted significantly increased amounts of follicle-stimulating hormone (FSH) in the urine. This hormone is biologically identical with that found in the urine of castrated or postmenopausal women. Hamburger[365] subsequently pointed out that its excretion does not cease after removal of the tumor and bears no relation to the presence or absence of metastases. Furthermore, this hormone has never been demonstrated in the tumors themselves or in their metastases. Therefore it is inferred that the FSH in these cases is of pituitary origin. Hamburger[336,365] also found a reduced urinary androgen excretion in these patients and attributed this to destruction of the testis by tumor irradiation or actual surgical removal. The increased gonadotropic activity in these cases is regarded by this author as a *hemicastration phenomenon secondary to testicular deficiency.* However, this explanation appears to be untenable since removal of one gonad from a male or a female does not bring on menopausal symptoms with increased pituitary gonadotropic activity. *It is more reasonable to agree with* Twombly[81] who conceives of a shift in hormonal balance with increased pituitary gonadotropin and decreased urinary androgen as a primary endocrine dysfunction which may lead to testicular tumor formation.

The nature and significance of urinary gonadotropins in testicular tumor.—As previously mentioned, patients with seminoma and teratoma of the testis may excrete large quantities of gonadotropic hormone in their urine. The hormone may be of the follicle-stimulating type or the interstitial cell stimulating type (chorionic gonadotropin of the type found in pregnant women's urine). *Rarely they may appear consecutively* or simultaneously in the urine. The FSH type occurs predominantly in patients with seminoma while the chorionic type is found most often in teratoma. The latter is apt to be present in large enough quantities to give a positive pregnancy test (Aschheim-Zondek or Friedman) when whole urine is injected into appropriate immature female animals. This is particularly

true in those teratomas and "mixed epitheliomas" which contain syncytial and trophoblast-like cells, i.e., chorionepithelioma. However it is important to recognize the fact that the absence of increased urinary gonadotropins does not exclude the presence of testicular tumor. Even a widely metastasizing tumor of the testis may occur without the excretion of detectable amounts of gonadotropin.

The nature of the FSH type of gonadotropin occurring in these patients has been discussed above. The chorionic type of gonadotropin can be demonstrated in extracts of chorionepithelioma and related tumor tissue.[365] Its excretion is roughly proportionate to the amount of tumor tissue in the body. Furthermore, it is not found in the pituitary of patients who excrete it. Its presence usually signifies a highly malignant, radioresistant tumor. In all these respects this gonadotropin differs from the FSH type and there is every reason to believe that it is formed by the tumor.

A clear distinction can be made between the follicle-stimulating and chorionic types of gonadotropin. This involves the use of biologic tests on hypophysectomized animals or normal immature mice and rats. Many methods have been employed but the most practical are those in which the hormonal effects on the ovary of the injected mouse are studied histologically. Injections of material containing FSH cause the ripening of many or all the follicles of the infantile ovary. Corpora lutea result only from large doses. Chorionic gonadotropin in dilutions just strong enough to give a positive reaction causes one or two large follicles to mature. Larger doses result in the formation of one or many corpora lutea atretica, occasionally with corpora hemorrhagica (Zondek II reaction). The technics of the various methods employed in the differentiation of the two types of gonadotropin including a most satisfactory procedure used in his laboratory has been described by Twombly.[81]

Hamburger[80, 36] attaches great importance to the differentiation between FSH and chorionic type of gonadotropin in the urine of these patients. He is of the opinion that such differentiation is of value in predicting the predominant histology of the tumor and therefore in prognosis. Although Hamburger found a close correlation between seminoma and FSH excretion on one hand and "mixed epithelioma" (teratoma, chorionepithelioma) and chorionic gonadotropin on the other, Twombly's[81] experience indicates frequent exceptions to this rule. Of 29 patients with chorionic gonadotropin in whom a pathologic diagnosis was possible, 10 were embryonal adenocarcinomas, 7 were chorionepitheliomas (Hamburger's "mixed epithelioma"), 9 were seminomas and 3 showed mixtures of seminoma and embryonal adenocarcinoma. Of 13 patients with follicle-stimulating hormone where a pathologic diagnosis was available, 2 were chorionepitheliomas, 7 were seminomas, 3 were adult cystic teratomas and 1 was a mixture of seminoma and embryonal adenocarcinoma. It is therefore apparent that while the histologic type of the tumor cannot be predicted accurately by gonadotropic assay of the urine there is nevertheless a frequency of association which cannot be denied. Twombly[81] believes that the discrepancies in which seminomas are accompanied by the excretion of chorionic gonadotropins can be explained by the fundamentally teratoid nature of all these testicular tumors as originally set forth by Ewing.[82]

Summary of the urinary hormonal pattern in testicular tumor — The majority of men with testis tumors excrete increased amounts of gonadotropin The FSH type is found more commonly in association with seminoma Its presence is independent of whether or not there is any active tumor present It is believed to be of pituitary origin The chorionic (pregnancy) type of gonadotropin is found predominantly in the urine of men with teratomatous tumors *It can be demonstrated only when active tumor is present* It disappears after the tumor is removed and its reappearance after an interval signifies the development of metastases Its presence generally indicates radioresistance and a very grave prognosis

The urinary excretion of estrogenic substances is occasionally elevated especially when there is a large quantity of chorionic gonadotropin being *formed*[80 81 36] *However, exceptions have been recorded*[338]

The excretion of free pregnanediol has been reported in one man with chorionepithelioma[81]

The excretion of biologically active androgens in the urine is sharply reduced in patients with seminoma of the testis In the presence of teratoma androgens are not decreased as often or as markedly although some *reduction is frequently observed On the other hand* androgens are probably excreted in excessive amounts in many cases of Leydig cell tumor although observations have been recorded in only one case

Although androgen excretion is low in most patients with testicular tumors the excretion of neutral 17 ketosteroids tends to be slightly increased In 1 case of Leydig cell tumor there was an extremely high level of 17 ketosteroid excretion

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Chapter 18

THE OVARY

EMBRYOLOGY OF THE FEMALE GENITAL SYSTEM ANATOMY OF THE FEMALE GENITALIA HISTOLOGY OF THE OVARIES OOGENESIS *HISTOLOGY OF THE ENDOMETRIUM AND VAGINAL MUCOSA*

By ARTHUR R SOHVAL M D

Introduction —Like the testis the ovary is concerned primarily with reproduction of the species This is accomplished by the formation of ova and the elaboration of an internal secretion The latter conditions the accessory genitalia as well as the secondary sexual characteristics The reproductive activity of the ovary differs from that of the testis in three important respects Firstly ovarian morphology and physiology have a distinctive periodicity during the period of sexual activity This results in marked cyclic alterations in the histologic anatomy and hormonal interrelationships of the female genital system which characterize the menstrual cycle Secondly the structural and functional integrity of the ovary undergoes a spontaneous regression at the time of the menopause Lastly the female must not only produce ova and sex hormones but must provide the locale for the fertilization of the ovum and implantation of the blastocyst The female is furthermore charged with the responsibility of nurturing and harboring the embryo during the entire period of gestation

These phenomena sharply contrast with the relatively non fluctuating activity of the testis which usually persists into the later decades of life The role of the male in the reproduction of the species is completed with the mere ejaculation of seminal fluid containing adequate numbers of viable spermatozoa

EMBRYOLOGY OF THE FEMALE GENITAL SYSTEM

A knowledge of the embryologic development of the ovary and accessory genitalia is essential for a better understanding of their anatomy and pathophysiology The reproductive system of both sexes has a common origin In its earliest stages the embryonal gonad possesses undifferentiated anlagen capable of development into either an ovary or a testis Similarly the young embryo contains both male (Wolffian) and female (Mullerian) sex ducts Differentiation of the primitive gonad into an ovary is accompanied by retention of the Mullerian duct system for purposes of ovum transport This results in the development of the accessory genitalia (fallopian tubes uterus and upper portion of the vagina)

The reproductive system in man originates in intimate association with the urinary system. The latter develops a few weeks earlier than the genital system and has been described in detail in the section dealing with the testis. Prior to separation of the urinary and genital systems they exist as a common mass known as the *urogenital system*. This extends longitudinally on either side of the dorsal mesentery for almost the entire length of the celomic cavity into which it bulges. This longitudinal ridge is known as the *urogenital ridge* and early subdivides longitudinally into a lateral *mesonephric ridge* and a median *genital ridge*.

According to Arey[1] the genital system appears somewhat later than the urinary system becoming evident during the fifth and sixth weeks (5 to 12 mm embryo). The medially placed genital ridge consists first of a thickening of the peritoneal epithelium which forms the *germinal epithelium*. Further proliferation of the germinal epithelial cells extends inward to form the *internal epithelial mass* which becomes the indifferent or undifferentiated sex gland.[2] Large distinctive cells lying both in the proliferating layer of germinal epithelium and within the internal epithelial mass may be recognized as *primordial germ cells*. There is considerable divergence of opinion regarding the origin of the primitive germ cells.[3] Although it would be logical to assume that they originate from the superficial proliferating layer of germinal epithelium, there is evidence suggesting that they may have migrated from distant sites. Similar cells have been observed in the yolk sac entoderm, gut entoderm and dorsal mesentery.[4] Not only is the origin of the primitive germ cells in the embryo a matter of controversy but the question of their origin during adult life is also in dispute. It is not known whether the primitive germ cells constitute the sole source of future germ cells or whether new germ cells appear as older cells degenerate.[5] Although there is evidence that germ cells differentiate from the superficial layer of germinal epithelium in certain mammals after puberty,[9,10] there is no convincing proof that this occurs in women.

The indifferent sex gland, consisting of a surface layer of germinal epithelium enclosing an internal epithelial mass which has proliferated from it, undergoes further development prior to differentiation. Columns or strands of cells known as *primary sex cords* appear within the substance of the gonad. These are generally believed to originate from the superficial layer of germinal epithelium[6] although Arey[1] is of the opinion that they organize themselves from the internal cell mass itself. The primary sex cords soon become separated from the overlying layer of germinal epithelium by a layer of connective tissue, the *tunica albuginea*. Development beyond this point proceeds along the lines of sexual differentiation into the male or female.

Ovary Differentiation.—The indifferent gonad destined to become an ovary shows identifiable changes at about the seventh week. This is slightly later than is the case for testis differentiation. The primary sex cords become radially disposed converging toward the hilum of the gland. They are now known as *medullary columns* and are arranged in a relatively dense *primary cortex* and a looser central *primary medulla* containing early primordial ova. At the same time a compact mass of epithelial cells extends into the *mesovarium* from the medulla with the formation there of the *rete*

ovarii (homologue of the rete testis) The mesovarium is the original mesentery of the mesonephros

According to Novak,[7] the primary sex cords soon disappear although vestigial rests may persist in the hilum in the region of the rete ovarii It is believed that from certain male-directed embryonal remnants in this region the masculinizing tumor of the ovary known as arrhenoblastoma may arise in later life

Concurrently with the disappearance of the primary sex cords (medullary columns) there is a rapid enlargement of the ovary This is due to the formation of *secondary sex cords* (of Pfluger) presumably as ingrowths from the actively proliferating surface germinal epithelium [8] This new cellular proliferation results in the formation of the *secondary cortex* of the ovary where the majority of cells become transformed into young ova In the meantime the earlier ova in the primary cortex and medulla degenerate resulting in the formation of the permanent medulla with its vascular fibrous stroma

The young ova (oogonia) are richly dispersed in the secondary cortex They persist and become surrounded by indifferent epithelial cells to produce the *primary follicles* Several hundred thousand are said to exist in each ovary at the time of birth[1,7] although the number undoubtedly varies widely

The encapsulating epithelial cells of the primordial follicles later become the *granulosa cells* of maturing follicles Another cellular component which appears later in this connection is the *theca cell* a specialized type of connective tissue cell Although the origin of both of these cells has not been definitely established the weight of evidence points to the ovarian mesenchyme itself[11,12,13] In Meyer's opinion[14] with which Novak[7] concurs superfluous masses or rests of indifferent epithelial cells may persist as a nidus for the formation of granulosa cell tumors of the ovary in later life A similar mechanism would account for the theca cell tumor of the ovary Furthermore a common origin of the progenitors of these two types of cells would explain the functional and histologic kinship of these two feminizing neoplasms [7]

The supportive connective tissue framework of the ovary appears early in the rete ovarii as an ingrowth from the mesovarium accompanied by a developing vasculature Extensions into the substance of the ovary form the interlacing stroma which fuses at the periphery as the *tunica albuginea* coat This layer of loose connective tissue not as well developed as it is in the testis lies just beneath the encapsulating layer of germinal epithelium Its formation in the three to four month old fetus precludes the further deposition of new cortex [1]

Development and Differentiation of the Female Genital Ducts —As previously stated the early human embryo possesses a sexually indifferent gonad and a double ductal system capable of differentiation into a female or a male genital tract Differentiation of the sexually indeterminate gonad into an ovary is accompanied by retention of the (Mullerian) duct system for purposes of ovum transport As the Mullerian duct extends caudad it turns medially to fuse with its mate from the opposite side to form *Muller's tubercle* The united lower portions of the Mullerian duct form

the uterus and upper vagina while the upper segment serves as the fallopian tube on each side At the same time that the Mullerian duct system undergoes transformation into the female accessory genitalia most of the male (Wolffian) component regresses Some of the cranially situated mesonephric tubules persist without function as the *epoophoron*, while others remain as the *vesicular appendices* The caudad group of tubules may be recognized in childhood as the *paroophoron* usually disappearing before puberty Although the major portion of the mesonephric duct degenerates a small vestigial remnant is found in about one fourth of females as the *duct of the epoophoron* or *Gartner's duct* The ultimate derivatives of the indifferent urogenital system are listed in Table 22 (p 412)

Descent of the Ovary —Like the testes the fetal ovaries are situated in the lumbar region near the kidneys Shortly before birth the ovaries gradually descend to the pelvic brim Sometime later the ovaries and uterus gradually reach their pelvic positions The total distance traversed by the ovaries in their descent is therefore not as great as that travelled by the testes A *gubernaculum* is attached to the ovary and probably plays an important role in guiding if not effecting the descent of the gland It extends from the ovary to the labium majus just as its counterpart in the male extends from the testis to the scrotum However where it courses near the uterus it becomes adherent to it This prevents the ovary from descending below this level In rare cases the gubernaculum fails to adhere to the uterus and the ovary continues its descent to pass through the inguinal canal into the labium majus In this event it comes to occupy a position analogous to that of the testis

The portion of the gubernaculum between the ovary and the uterus ultimately becomes the *ligament of the ovary* The portion extending from the uterus to the labium majus forms the *round ligament of the uterus* A shallow peritoneal pouch frequently accompanies the round ligament in the inguinal canal This is known as the *canal of Nuck* and is homologous with the processus vaginalis in the male

ANATOMY OF THE OVARY

The Gross Anatomy of the Ovary —The ovaries are grayish pink nodular bodies situated one on either side of the uterus They are ovoid in shape have a smooth or puckered surface and each measures about 4 cm in length 2 cm in width and about 8 mm in thickness The weight varies between 4 and 8 gm Its position varies with the posture of the subject being almost vertical in the erect position Each gland has an upper or tubal pole a lower or uterine pole a lateral and a median surface and a free posterior border The anterior border is attached to the posterior aspect of the broad ligament by a short *mesovarium* The vascular and nerve supply of the ovary reach the hilum between the layers of this structure

The upper pole is attached to the fimbria of the fallopian tube by a peritoneal fold the *suspensory ligament of the ovary* containing the ovarian vessels The lower pole is attached by its proper *ligament of the ovary* to the lateral aspect of the uterus just below and behind the attachment of the fallopian tube The ovarian ligament is contained within the substance

of the *broad ligament*. The latter passes from each side of the uterus to the lateral wall of the pelvis.

The blood supply is derived from branches of the ovarian and uterine arteries. These enter the medulla of the ovary at its hilum. Small branches penetrate the cortex, break up into capillaries and supply the theca of maturing follicles but not the granulosa. The venous return develops into extensive plexuses in the medulla and leaves the ovary at the hilum as the ovarian vein.

The lymphatic drainage likewise passes through the hilum of the ovary into a number of lymphatic trunks which enter the lumbar lymph nodes. Lymphatic channels are plentiful in the theca externa of the follicles as well as the corpora lutea and albicans. The internal theca layer, the granulosa and the tunica albuginea are free of lymphatics.

The nerves are derived from the hypogastric or pelvic plexus to form the ovarian plexus. These nerves are chiefly nonmyelinated and follow the course of the blood vessels.

THE HISTOLOGY OF THE OVARY

There is little change in the microscopic anatomy of the ovary during the prepuberal era. With the onset of puberty the ovary begins to assume an all important role in the reproductive activity of the individual. Approximately once a month a primary ovarian follicle is singled out to grow, mature, discharge an ovum and be converted into a corpus luteum. The ovary thus enters upon a period of cyclic activity which lasts for thirty or thirty five years until the advent of the menopause. Once a month during this child bearing period either ovary ovulates. Usually the ovaries alternate in this function. Ovulation occurs most frequently about two weeks after the beginning of the cycle although there is a considerably wide variation in the timing of this event. It is thus apparent that the histology of the normal ovary is in a constant state of flux, contrasting sharply with the testis in this respect. The underlying hormonal mechanisms and interrelationships are discussed in the section dealing with the physiology of the ovary (Chapter 19).

Upon examination of a cross section it is seen that the ovary is composed of a broad outer layer, the *cortex*, and a central portion known as the *medulla*. According to Baily[15] the medulla is composed of a stroma of loose connective tissue containing many elastic fibers, blood vessels, lymphatics and nerves. In the hilum of the ovary there are, in addition, smooth muscle fibers and occasionally epithelial strands of embryonal origin known as the rete ovarii.

The cortex comprises one-half to two thirds of the ovarian substance during the child bearing span of a woman's life. Within the cortex are situated the very numerous *ovarian follicles* separated by a fairly compact richly cellular stroma. Superficially the connective tissue elements of the stroma fuse to form the *tunica albuginea*, a structure considerably less dense than its counterpart in the testis. Enveloping the entire surface of the ovary except at the hilum is the layer of *germinal epithelium*. This is continuous with the peritoneal mesothelium and consists of a layer of cuboidal

cells which is often well preserved in the ovaries of children but usually disappears during adult life.[7]

The Ovarian Follicles. — At the time of birth the cortex of each ovary contains a large number of primitive follicles variously estimated at between 40,000 to 400,000.[1,15] Each follicle consists of one large ovum (oogonium) measuring about 20 microns in diameter surrounded by a flattened or low cuboidal layer of epithelium, the *membrana granulosa*. Although the newborn infant's ovaries are endowed with an abundance of primitive follicles only relatively few ever reach maturity. When one considers the fact that one ovum matures each month during the thirty-odd years of woman's active sexual life it is apparent that less than 500 follicles attain maturity during a lifetime. The majority of the primitive *follicles undergo degeneration (atresia) which is completed a few years* after the menopause.

Not much alteration occurs in the primitive follicles until the subject reaches puberty. During the prepuberal period *early* growth of some follicles is noted with enlargement of the oogonium and an increase in the number of surrounding follicle cells. With the advent of puberty, largely under the influence of adenohypophyseal gonadotropic hormone stimulation, the *later* development of certain follicles occurs enabling them to attain complete maturity, resulting in the expulsion of an egg and the formation of a corpus luteum. During a woman's active reproductive period (extending from puberty to menopause) the ovary contains follicles in all stages of growth and development. As a follicle matures it pushes more deeply into the substance of the ovary. Growth of the follicle is accomplished by a proliferation and stratification of the follicular (granulosa) cells, an increase in the size of the ovum and the formation of a connective tissue capsule.[15] With continued growth a central cavity or *antrum* appears. This becomes filled with the estrogen-containing secretion of the follicular cells, the *liquor folliculi*. The follicle is now known as a *vesicular follicle*. The ovum is pushed aside becoming eccentrically situated at one pole of the follicle. It is surrounded by a hillock of granulosa cells, the *cumulus oophorous* or *discus proligerus*. Surrounding the granulosa lining of the follicle is a highly vascular layer of connective tissue cells, *the theca interna*. Although the cells of the theca interna are of connective tissue type they later assume an epithelioid appearance (theca lutein cells) under the influence of hormonal stimulation.[7] A condensation of the ovarian stroma develops around the entire follicle to form its *theca externa*.

As the follicle matures the contained ovum rapidly increases in size. In the human it attains a diameter of 100 to 150 microns in the *mature* or *Graafian follicle*.[18] The latter finally reaches a diameter of about 10 mm when fully grown and occupies the entire width of the cortex. At the height of its maturity the Graafian follicle produces a slight bulge on the surface of the ovary, the *stigma*. It is through this thinned-out avascular area of the theca and tunica albuginea that the follicle will eventually rupture and discharge its ovum. This is known as *ovulation* and its underlying mechanisms are not definitely known. Concerning the various etiologic possibilities, Novak[7] is of the opinion that a local enzyme-like erosion effect is the most likely. The relative importance of increasing tension of

the follicular fluid and contraction of surrounding muscle fibers have not been elucidated as yet It is believed[18] that rupture occurs gradually rather than cataclysmically

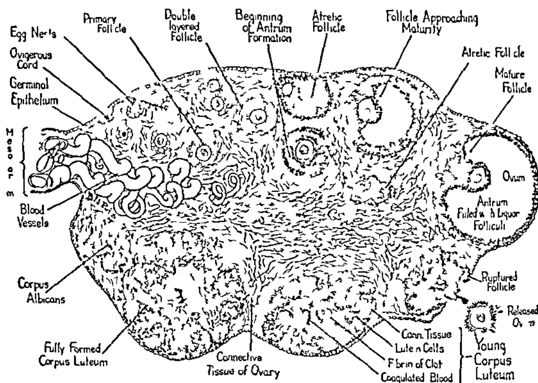


FIG 47 – Schematic drawing of a mammalian ovary tracing the sequence of events from the earliest formation of the primary follicle through its maturation The transition after rupture into the corpus luteum and its eventual involution are also depicted Follow clockwise around ovary starting at mesovarium (From Patten Human Embryology Courtesy of The Blakiston Company)

Immediately prior to its discharge the ovum is embedded in a well-developed cumulus oophorous (discus proligerus) composed of an aggregation of granulosa cells Those cells immediately surrounding the ovum are arranged radially and are known as the *corona radiata* This layer of cells remains attached to the ovum after it is discharged Subjacent to the corona radiata is the *zona pellucida* an amorphous refractile membrane A very narrow *perivitelline space* exists between this and the ovum The cell membrane of the ovum itself is known as the *vitelline membrane* The nucleus of the ovum is the *germinal vesicle* and its nucleolus the *germinal spot*

Following ovulation the discharged ovum with its attached corona radiata measures about 150 microns in diameter These proportions render it barely visible to the naked eye It must be fertilized by a spermatozoon rapidly or it will degenerate It is probable that the time limit for viability in the unfertilized state does not exceed twenty four hours Fertilization occurs at or near the fimbriated end of the fallopian tube It has been

shown by Hertig and Rock[16] that the fertilized ovum reaches the uterus about three days after ovulation Implantation of the blastocyst in the endometrium occurs two to five days later

The Corpus Luteum of Menstruation.—After ovulation the ruptured follicle is transformed into the corpus luteum which undergoes a series of progressive changes The stigma through which the egg was extruded becomes sealed and there is usually little or no bleeding [7] The granulosa cells enlarge their nuclei become vesicular and their cytoplasm contains large amounts of yellowish lipoid pigment (lutein) These are the *granulosa lutein* cells They appear as a stratified lining of large pale staining cells and characteristically cause the lutein layer to be thrown into folds about the central cavity At the same time the corpus rapidly becomes vascularized by an ingrowth of delicate vessels from the theca layer As these reach the central cavity they may partially fill it with blood Cells from the theca interna layer tend to migrate along with the new blood channels They now assume an epithelioid character and since they too contain fatty droplets they probably have an endocrine function Because of their resemblance to the granulosa lutein cells they are called *theca-lutein* or *paralutein* cells [7] The distinctive bright orange color of the human corpus luteum is due to the pigment content of the combined mass of lutein cells The latter elaborate the characteristic hormone of the corpus luteum *progesterone* This hormone is secreted in addition to the *estrogenic hormone* which continues to be secreted as it was during the preovulatory phase of the follicle

The corpus luteum reaches its maturity about one week before the next menstrual period At this time its diameter is between 1 and 2 centimeters The central cavity is usually small has a very irregular outline and contains serous fluid or fibrin from old blood together with a loose connective tissue Concomitant with the vascularization of the corpus luteum there is a progressive extension of connective tissue from the theca layer into the lutein mass This finally comes to cover the inner surface of the broad festooned lutein layer separating it from the central cavity [7]

In the absence of implantation of the fertilized ovum the well-developed corpus luteum begins to degenerate shortly before the next menstrual flow This is characterized by accumulations of lipids resorption of the lutein cell and increasing fibrosis The corpus becomes progressively smaller in size as the entire mass becomes cicatrized and hyalinized It is now known as a *corpus albicans* appearing as a tiny whitish scar The process of involution requires several weeks or months to complete

The Corpus Luteum of Pregnancy—When the previously discharged ovum is fertilized and pregnancy ensues the corpus luteum becomes larger instead of retrogressing It may attain a diameter of 2 to 3 cm and thereby comprise a substantial portion of the ovarian mass The central cavity also attains a comparatively large size The corpus remains active until the second half of gestation when it undergoes involution by a process similar to that described for the corpus luteum of menstruation Calcific deposits may appear in the degenerated mass [17]

Atresia of Follicles—Of the large number of follicles present at birth in the ovaries of the human female only a few reach maturity and discharge the

the follicular fluid and contraction of surrounding muscle fibers have not been elucidated as yet It is believed[15] that rupture occurs gradually rather than cataclysmically

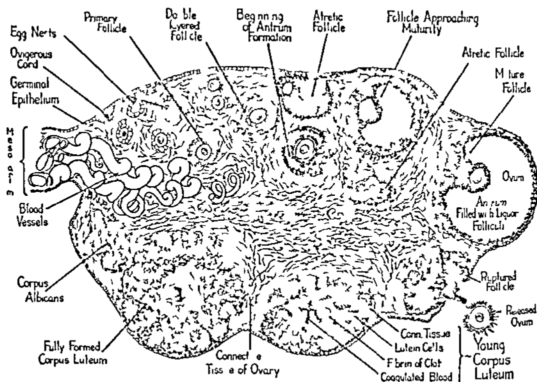


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full development. Only in the mature Graafian follicle is the fully grown *primary oocyte* found. It generally measures about 140 microns in diameter, the latter having increased about seven fold in size. The primary oocyte must now complete two maturation divisions in order for its chromosomal content to be halved. These two cellular divisions occur by an atypical method called *meiosis* in distinction to the usual method of cell division by mitosis.

As a result of the first meiotic division the primary oöcyte gives rise to a *secondary oocyte* and a *polar body* (the first). This meiotic division is called *reductional* since it is characterized by simple separation of a pair of chromosomes and is *qualitative* in nature. Each daughter cell contains an equivalent number of chromosomes but not an equivalent genic composition. While the nuclear chromatin is divided equally the division of the cytoplasm is extremely unequal. For this reason the bulk of the germ plasm remains in one daughter cell (the secondary oocyte) while only a minute amount passes to the other cell (the first polar body) which in most species soon degenerates without undergoing further division.

In the second meiotic division each single chromosome of the original pair splits (as in ordinary mitosis) and one half passes into each of two daughter cells. This division is termed *equational* and is *quantitative* in that the two *halves are identical in all respects. This type of division is of course* quite different from the reductional or qualitative type of meiotic division by which separation of a pair of chromosomes results in daughter cells *which contain different genes derived from either parent*. The second meiotic division is also characterized by the formation of two daughter cells which are markedly unequal in size. As a result of this division the secondary oocyte gives rise to the *mature ovum* (ootid) having a diameter of about 130 microns and a *second polar body*. It is not known whether the second division of meiosis occurs before or after rupture of the Graafian follicle in the human. Allen and his collaborators[45] obtained an oocyte which they believe could have been discharged prior to the final stage of oogenesis. In most mammals the first polar body is formed in the ovary while the second is cast off after ovulation.[1] This may very well occur after fertilization.

Of the 48 chromosomes present in all somatic and immature germinal cells of the human species two are concerned with the determination of sex. These are the X- and Y chromosomes, the X being the important sex chromosome. Two X chromosomes are present in all somatic and primitive germ cells of the human female whereas only one X-chromosome and a small inert Y-chromosome occur in the cells of the male. During the first meiotic division in the male the pair of chromosomes separate so that two different sexually constituted secondary spermatocytes are formed, one *containing 23+X and one having 23+Y chromosomes*. In the female of course each secondary oocyte is sexually equivalent, possessing the 23+X combination. The sex of the fertilized egg will depend upon whether fertilization occurred by a 23+X or 23+Y *sperm, the former will result* in a female (46+2X) whereas the latter produces a male (46+X+Y). Thus it is evident that the sex of the offspring is determined by the chromosomal content of the male gamete.

ovum The vast majority degenerate either as primary follicles or during various stages of growth Degeneration of the follicles occurs by a process of atresia which takes place continuously before and after puberty Atresia of primary follicles results in lysis and fragmentation of the ovum and the narrow zone of surrounding follicle epithelium Fibrous replacement of the destroyed follicle usually leaves no traces

During the period of sexual maturity many follicles begin to mature and develop antra with each menstrual cycle However only one "favored follicle" is destined to go on to complete maturity terminating in ovulation and corpus luteum formation The remainder undergo degeneration at various stages of development Resorption of antrum-containing follicles is more time consuming and less complete than is the case with primary follicles Death of the ovum and degeneration of the granulosa cells proceeds as in the undeveloped follicle While the cells of the theca interna also degenerate in the larger follicles they may at times enlarge and form a compact layer around the follicle The central cavity may then become cystic and such ovaries may present numerous tiny follicular cysts (microcystic ovaries)

After the menopause the remaining primary follicles gradually undergo atretic degeneration Within a few years undegenerated follicles are no longer to be seen

Oogenesis — The process by which primitive oogonia develop into mature ova is known as oogenesis It is comparable to spermatogenesis in the male each process producing sexual maturity in the respective sex The process in the two sexes differs in that oogenesis terminates spontaneously with the menopause whereas spermatogenesis often persists into old age Another difference lies in the fact that in the male each primary spermatocyte produces 4 mature spermatozoa In the female each primary oocyte produces only 1 functioning ovum The remaining 3 products of cellular division are the non functioning minute polar bodies

Apart from striking morphologic and numerical differences in the maturation of ova and spermatozoa the genetic mechanisms involved are identical The maturation of germ cells regardless of sex accomplishes a very definite objective in preparing them for union This involves a halving of the somatic number of chromosomes so that fertilization of an ovum by a spermatozoon restores the normal number of chromosomes

The gametogenic mechanism of ovum development consists of a preliminary stage of *cell proliferation* a period of *growth* of the proliferated cells and a final stage of *maturation* It is in the final stage of maturation that the last two cellular divisions result in a sexual gamete containing but one half of the original number of chromosomes (Fig 35 p 418)

The period of proliferation is completed at the time of birth The ovaries of the newborn baby contain their permanent full complement of primitive ova or *oogonia* each measuring about 20 microns in diameter These arise by the usual process of mitotic division and each germ cell contains 48 chromosomes the normal number for the human species

The period of growth takes place as the primitive follicle enlarges under adenohypophyseal gonadotropic stimulation As previously described many growing follicles and their contained ova degenerate before attaining

that portion which extends above the entrance of the fallopian tubes is known as the *fundus* The outlet of the uterus the cervix communicates with the vagina through the *external os* The uterus is composed of an outer layer continuous with the peritoneum and the broad ligament, a middle muscular layer the *myometrium* and an inner glandular coat known as the *endometrium* The latter is partly shed during menstruation

Enclosing the distal end of the uterus is the *vagina* which forms practically a right angle with it It is 6 to 7 5 cm in length on its anterior wall and 9 cm along its posterior wall It courses upward and forward toward the vestibule It is lined by a stratified squamous epithelium encircled by a thin muscular wall In the virginal state the external orifice is partially occluded by a membranous hymen

The external genital organs include the labia majora labia minora, the clitoris and the glands of Bartholin These are contained within the *vestibule* which is a groove extending from the pubic pad of fat (*mons veneris*) toward the anus The *labia majora* are two prominent folds of skin which bound the openings of the vagina and urethra They are homologous with those structures in the male which unite to form the scrotum Just within these two large folds are two smaller *labia minora* the anterior extremities of which encircle the clitoris The clitoris is an erectile structure homologous with the penis lying just above the urethral orifice *Bartholin s glands* are the homologues of the bulbo-urethral (Cowper s) glands in the male *They are situated one on each side of the vaginal opening* A single excretory duct is to be found in the groove between the vagina and the labium minora on each side

THE HISTOLOGY OF THE ENDOMETRIUM

Concurrently with the cyclic changes in the ovaries of woman during her child bearing span there are cyclic changes in the endometrium There is an abundant accumulation of experimental and clinical data indicating a specific correlation between ovarian and endometrial cycles The state of the uterine mucosa is dependent upon that of the ovary In other words the endometrial picture is determined by the constantly changing pattern of the ovarian hormonal secretions The preovulatory phase of ovarian follicle development is characterized by *a gradually increasing production* of estrogenic hormone This is responsible for the proliferative phase of the endometrium following menstruation After ovulation the follicle is converted into a corpus luteum Progesterone is now secreted along with estrogenic hormone This results in certain changes in the endometrium known as the secretory phase With regression of the corpus luteum (and reduction in hormone formation) the endometrium begins to disintegrate and most of it is shed during menstruation

The cycle is repeated after menstruation when estrogenic hormone is again produced in increasing amounts by one or more newly-developing ovarian follicles From the remaining basal layer of endometrium a completely new functioning layer regenerates If the recently discharged ovum becomes fertilized and implanted into the endometrium the latter

The Ovarian Stroma or Interstitial Tissue — The ovarian follicles are embedded in a stroma of connective tissue consisting of a network of collagenous, elastic and reticular fibers. The spindle-shaped connective tissue cells are closely packed in the cortex but the entire mesenchymal structure is more loosely arranged in the medulla. The principal interstitial cell is the fibroblast. In the human no true secretory interstitial cell comparable to that of the testicular Leydig cell has been described in the stroma of the cortex. This is not true in certain mammals where the cortical stroma contains clusters of epithelioid connective tissue cells with lipoid droplets in their cytoplasm suggesting a hormonal function. In the cat these interstitial cells are derived from the theca cells of degenerating follicles. In other species interstitial cells may originate from invaginations of the germinal epithelium or possibly by cell multiplication in situ.[23] Kingsbury,[4] however, interprets the accumulation of lipoids in these cells as an evidence of storage rather than secretion.

The stroma at the *hilum* is especially loose and is traversed by the blood vessels, lymphatics and nerves which enter and leave the ovary. It often contains certain embryonal remnants such as the rete ovarii and the paroarian tubules. The former are derived from the fetal primary medulla and appear as narrow, slit-like tubules lined by a flat epithelium. The latter are vestiges of Wolffian tubules. They usually appear in clusters, are lined by cuboidal epithelium and are surrounded by a muscular coat.

Certain nests of large epithelial cells in intimate contact with nonmyelinated nerve fibers have been described in the hilum of the ovary and mesovarium by Berger.[18,19,20] These have been termed "sympathicotropic cells" or "hilus cells." They contain crystalloids which are morphologically and histochemically indistinguishable from the Reinke crystalloids of testicular Leydig cells. They are thought by Berger and others[1,22] to be identical with Leydig cells and are regarded as the probable source of male sex hormone which can be extracted from the ovary. In some instances they are believed to be the origin of certain masculinizing tumors known as Leydig cell or hilus cell tumors of the ovary.[19,21,72]

THE FEMALE ACCESSORY GENITALIA

The accessory internal organs of reproduction consist of two fallopian tubes, a uterus and a vagina. The *fallopian tubes* are situated one on each side to convey the extruded ovum to the uterus. Each tube measures about 10 cm in length. Its lateral extremity is broad and funnel shaped. It is known as the *infundibulum* and is surrounded by finger-like projections called fimbria. These are in close approximation to the ovary and facilitate passage of the egg to the fallopian tube. Medially, the fallopian tube enters the uterus at its upper lateral margin. The entire length of the fallopian tube is supported by the *mesosalpinx*. This is the portion of the broad ligament which stretches from the fallopian tube to the level of the ovary. The *uterus* is a pear-shaped, hollow, muscular organ suspended in the broad ligament. It is divided into an upper *body* and a lower *cervix*. The body or corpus of the uterus is flexed anteriorly at the *isthmus* and

ation initiates the process of repair. This phase continues from the termination of bleeding, about the fourth day, until the occurrence of *ovulation* at about the fourteenth day of a typical twenty eight day cycle. The development of the endometrium during this phase is due to the influence of increasing amounts of estrogenic hormone which is being secreted by the maturing Graafian follicle as well as by its satellite follicles. The regenerative process takes its origin from the narrow basal zone of endometrium which remains after menstruation. This is only 1 or 2 millimeters thick. The continuity of the surface epithelium is quickly restored by low cuboidal cells. The glands, lined by the same type of epithelial cells, are short, straight and narrow. The stroma is dense and relatively avascular.



Fig 48.—Endometrium in the early proliferative phase (fifth day of the cycle). The surface and glandular epithelium is lined by cuboidal or low columnar cells. The glands are narrow and straight. The stroma is relatively dense. (From Novak, Menstruation and Its Disorders, D. Appleton-Century Co.)

Soon mitoses become evident in the epithelial and stromal cells heralding the considerable proliferation which is to follow. The epithelial cells of the glands and surface of the endometrium become taller and definitely columnar. The glands increase in length and become somewhat wider although they are still relatively straight. The stroma participates in the growth reaction becoming wider but looser in texture due to the presence of some edema. The spiral arterioles gradually grow into the newly proliferating endometrium so that at mid-cycle they extend through one half

does not regress but develops into a markedly hypertrophic state which adapts it for pregnancy. Teleologically, the progressive endometrial changes which characterize the menstrual cycle are ordained by the ovaries in anticipation of possible fertilization of an ovum. When this fails to occur, most of the recently prepared endometrium is discarded with the menstrual flow and the process starts anew. It is therefore evident that the microscopic anatomy of the normal postpuberal endometrium undergoes constant change.

Basically the endometrium consists of a specialized type of connective tissue lined by simple cuboidal or columnar epithelium. The latter is continuous with the lining of many simple tubular glands which extend from the surface into the deepest portions of the endometrium. The stroma between the glands consists of connective tissue cells embedded in a delicate supporting fibrillary tissue containing capillaries, arterioles, venules and arteriovenous anastomoses. The character of the vasculature varies markedly with the functional activity of the endometrium. There is no submucosa, the endometrium being in direct contact with the myometrium. Three layers of endometrium can be recognized at various stages of the cycle. The deepest layer, the *basalis*, *does not participate in the cyclic changes* and is relatively narrow. The remainder of the endometrium reflects all of the functioning phases of the membrane and is therefore termed the *functionalis*. Most of it is shed during menstruation and parturition. Its maximum development is attained in the second half of the menstrual cycle. During this stage a superficial narrow dense zone is called the *compacta*, while the deeper looser region forming the bulk of the endometrium is known as the *spongiosa*.

The blood supply of the endometrium is highly specialized and especially adapted to its periodic requirements. It consists of two systems of arteries derived from a common branch of the *arcuate artery*, the latter being a branch of the uterine artery. As the nutritional artery approaches the endometrium it divides into a short straight *basal arteriole* which supplies the basal layer of the endometrium[5] and a *spiral or coiled arteriole* which enters the functioning layer.[31] The blood supply of the two zones of the endometrium is therefore quite independent. The coiled arterioles participate actively in the cyclic endometrial changes, while the basal arterioles undergo no important fluctuations.

The constantly changing histology of the endometrium during the course of the menstrual cycle is conditioned by important changes in the surface and glandular epithelium, the vasculature and the stroma. While it is recognized that the evolution of the endometrium during a menstrual cycle is gradual and lacking in sharp transitions, it is a matter of practical and didactic value to divide the entire cycle into a *proliferative*, a *secretory* and a *bleeding phase*. Although a normal menstrual cycle may range from three to five weeks in duration the majority of cycles strike an average of twenty eight days. By universal agreement the first day of the cycle is counted from the first day of the menstrual flow.

The Proliferative Phase.—This is also known as the follicular, preovulatory or early interval phase. Even during and quickly following the endometrial sloughing which occurs during menstruation, epithelial regener

ation initiates the process of repair. This phase continues from the termination of bleeding, about the fourth day, until the occurrence of *ovulation* at about the fourteenth day of a "typical" twenty-eight day cycle. The development of the endometrium during this phase is due to the influence of increasing amounts of estrogenic hormone which is being secreted by the maturing Graafian follicle as well as by its satellite follicles. The regenerative process takes its origin from the narrow basal zone of endometrium which remains after menstruation. This is only 1 or 2 millimeters thick. The continuity of the surface epithelium is quickly restored by low cuboidal cells. The glands, lined by the same type of epithelial cells, are short, straight and narrow. The stroma is dense and relatively avascular.



Fig. 48.—Endometrium in the early proliferative phase (fifth day of the cycle). The surface and glandular epithelium is lined by cuboidal or low columnar cells. The glands are narrow and straight. The stroma is relatively dense. (From Novak: Menstruation and Its Disorders, D. Appleton-Century Co.)

Soon mitoses become evident in the epithelial and stromal cells heralding the considerable proliferation which is to follow. The epithelial cells of the glands and surface of the endometrium become taller and definitely columnar. The glands increase in length and become somewhat wider although they are still relatively straight. The stroma participates in the growth reaction becoming wider but looser in texture due to the presence of some edema. The spiral arterioles gradually grow into the newly proliferating endometrium so that at mid cycle they extend through one half

or two-thirds of its thickness. At the same time they become somewhat more coiled. This is due to the disproportion between the increasing length of the arterioles and the thickening endometrium. Toward the end of the proliferative stage the nuclei of the glandular columnar epithelial cells become displaced toward the lumens by the formation of subnuclear vacuoles. These clear areas situated at the base of the cells are the first indications of a beginning secretory activity. Concurrently the glands become tortuous. At the conclusion of the proliferative phase the endometrium measures about 2 to 3 millimeters in thickness (Figs. 48 and 49).

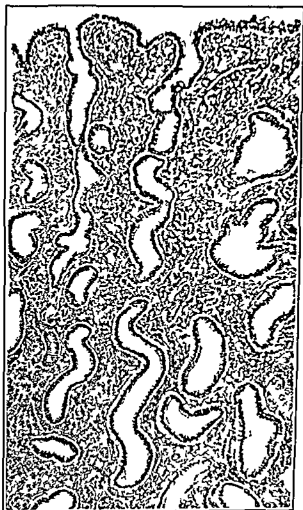


Fig. 49.—Endometrium at the end of the proliferative phase (fifteenth day of the cycle). The epithelial cells are taller and more columnar. The nuclei of the glandular cells are displaced away from their basal position toward the lumen by subnuclear vacuoles which have just formed. The glands are wider and becoming tortuous. The stroma is less dense. (From Novak: Menstruation and Its Disorders, D. Appleton-Century Co.)

The Secretory Phase.—This stage is also termed the luteal, postovulatory, progestational or late interval phase. It develops imperceptibly from the proliferative phase at the time of ovulation and reaches maximum development from a few days to a week before the next menstrual flow. It is characterized by an increasingly marked secretory activity of the glands as well as by increased edema and blood vessel development. These changes are due to the influence of progesterone which is now being secreted by the corpus luteum of the ovary in addition to estrogen. At the height of its development the endometrium attains a width of four to six millimeters. The glands hypertrophy markedly, becoming larger, wider and more tortuous, assuming a corkscrew shape. In the deeper portions they become

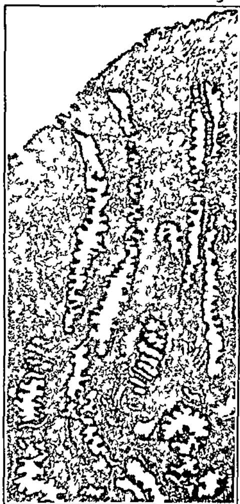


Fig. [illegible]0.—Endometrium in the late secretory phase (twenty-fifth day of the cycle). The markedly hypertrophied glands are dilated and tortuous and have a serrated border. (From Novak: Menstruation and Its Disorders, D. Appleton-Century Co.)

sacculated. Their borders on section present a serrated appearance. The lining epithelial cells show further development of the subnuclear vacuoles. By special staining technics, these are known to be due to inclusions of glycogen and mucin, an index of secretory activity. As the development of this stage progresses the epithelial cells of the glands become lower, the nucleus resumes its former basal position and the vacuoles push toward the lumen of the glands. The free surface of the epithelium assumes a wavy frayed appearance. The lumens of the glands contain glycogen and mucin. The portions of the glands which extend into the basal layer of the endometrium do not participate in these cytologic evidences of secretory activity (Fig. 50).

During the development of the secretory phase the spiral arterioles become thicker, more coiled and extend closer to the surface epithelium. *The stroma increases in width largely through edema.* *According to* Novak[7] the stromal cells in the proliferative phase consists almost entirely of nucleus with very scant cytoplasm. As the maximum secretory phase is attained just prior to menstruation these cells develop a well-defined cytoplasm. At times cell hypertrophy may be so great as to resemble very closely the decidual cell of early pregnancy. The disposition of the stromal components toward the latter part of the secretory phase leads to a division of the endometrium into 3 layers. The superficial layer is the narrow, closely packed *compacta*. The deepest layer is the non-participating *basalis*. The bulk of the membrane is composed of the edematous intermediate zone, the *spongiosa*.

Within a variable numbers of days prior to menstruation regressive changes appear in the secretory endometrium. These are believed by Markee[34] to result primarily from a "withdrawal" of estrogen although the possible involvement of progesterone in this mechanism cannot be denied. The fall in available estrogen and progesterone during the premenstrual phase is due to a decline of corpus luteum activity. The latter undergoes involution when the previously discharged egg fails to be fertilized. The stroma decreases in width due to partial absorption of edema.[46] This results in a diminution in the thickness of the membrane. At the same time a rather intense infiltration with polymorphonuclear leucocytes appears. One of the most striking and important alterations which occurs *premenstrually is that involving the vasculature.*

The spiral arterioles now contained in a narrower layer of endometrium undergo buckling and mechanical obstruction to the flow of blood. According to Markee[6] this accounts for the premenstrual stasis which precedes degeneration of the endometrium. Venous and capillary congestion contribute to the slow rate of bloodflow. Recent studies by Okkels[33] and his collaborators point to the presence in the premenstrual endometrium of an additional important vascular alteration. This is the establishment of arteriovenous anastomoses which shunt *the arterial blood supply directly* into channels for venous return. In this manner the superficial layers of the endometrium are by passed. The net effect on the capillaries within these layers depends upon two different factors. The first is interference with the return flow of blood which results in vascular stasis. The second is a deprivation of blood flow into the superficially situated capillaries resulting in ischemia. These changes explain the hysteroscopic observations of

Hisner[32] and Schroeder[47] who noted a bluish pink and a blanched mucosa at various times during the premenstrual phase

The Bleeding or Menstrual Phase — This usually lasts from three to five days with an average of four. It is the natural outcome of an ovarian cycle when failure of egg fertilization occurs. As shown by Markee[6,27,33,34] it is associated with and probably due to a *sudden* withdrawal in the amount of circulating estrogenic hormone. The anatomic changes to be described occur in anovulatory as well as ovulatory cycles. They are independent of whether or not a true secretory phase (due to progesterone) preceded the bleeding phase.

Novak and Te Linde[30] have shown that this phase results in the desquamation of the compacta and a variable amount of the spongiosa layer. The basalis remains intact by virtue of its independent blood supply and acts as a foundation upon which the postmenstrual process of regeneration depends. Sloughing may be spotty and irregular at the beginning but usually involves the entire mucosal surface by the second day. In rare instances a complete cast of the uterine mucosa may be desquamated at one time.[7]

The dynamic relation of the endometrial vasculature to the onset of menstruation has been the subject of considerable study. The ingeniously contrived observations of Markee[6,7,33,34] have proved invaluable in the elucidation of the vascular and hormonal mechanisms involved in the phenomenon of menstruation. Their physiologic significance is discussed in a later section. Homotransplants of macaque endometrium into the anterior chamber of the eye were examined daily during hundreds of cycles. The transplanted endometrium was examined in situ in the unanesthetized animal through the transparent cornea by means of the naked eye and the microscope. The transplants menstruated simultaneously with the intact uterus and structural changes in its vasculature were carefully studied. Since cyclic changes in the macacus monkey's uterus are fundamentally the same as in that of woman,[29] Markee's observations can be accepted as being valid for the human as well.

The vascular changes immediately preceding menstruation were described above. They consist essentially of vascular stasis and congestion which Markee attributes to a mechanical buckling of the coiled arterioles. This is followed by anoxia, degeneration and necrosis of the surrounding endometrial epithelium and stroma. At the same time the vessel walls themselves undergo certain degenerative changes[27] which inevitably lead to diapedesis and rupture. This results in the formation of numerous small individual hemorrhages. These may appear in the stroma as hematomas or may escape through the disintegrating surface epithelium as free blood. The bleeding is controlled by constriction of those segments of the coiled arterioles which lie adjacent to the myometrium.[35,36] Temporary relaxation of the vasoconstricted segments from time to time permits a resumption of bleeding from the weakened walls of the distal portions of the arterioles. The phenomenon of alternate constriction and relaxation of the proximal portions of the coiled arterioles does not involve all the vessels simultaneously. A few vessels at a time relax so that bleeding occurs irregularly from multiple discrete foci.

Bleeding also occurs from congested capillaries and venules. This is not as brisk as that emanating from the arterioles. Blood which pools in

the substance of the stroma finds its way into the lumen of the uterus as the surface of the latter is gradually denuded

In addition to the grossly *bloody content of the menstrual discharge* the latter also contains the mucinous discharge of the endometrial glands and considerable cellular debris The fluid as a whole does not clot because of the presence of a fibrinolytic agent

THE HISTOLOGY OF THE VAGINAL MUCOSA

From an endocrinologic standpoint the microscopic anatomy of the vaginal mucous membrane is important because of its responsiveness to the ovarian hormones It is a matter of considerable practical interest that epithelial cells exfoliated from the vaginal mucosa reflect its state of functional activity However there has been much conflicting opinion as to whether or not cyclic histologic changes occur in the human vaginal mucosa as they do in some animals

In 1927 Dierks[37] drew attention to cyclic fluctuations in the histology of the vaginal membrane He described 3 epithelial layers a superficial *functionalis* an *intermediate cornified layer* (zone of intra epithelial condensation) and a deep *basalis* He observed all of the superficial and part of the intermediate layer to be shed during menstruation and attributed the cornification to a hormonal influence Other workers including Stieve[38] and Zondek and Friedmann[39] could find no evidence of definite cyclic alterations although the 3 layers described by Dierks constitute an accurate representation of the histologic anatomy The cells of the deepest or basal layer are small round or oval and have relatively large hyperchromatic nuclei As the intermediate zone is approached the cells become larger the nuclei smaller and the long axes come to lie parallel to the basement membrane When this layer is cornified the cells are quite flattened with small pyknotic nuclei and thick keratinized cell walls The superficial zone is composed of several layers of larger typical squamous cells

The majority of observers believe that some form of cyclic modification of the vaginal mucosa is manifested during the reproductive cycle but even here there is disagreement as to the nature and timing of the changes Geist[40] found cyclic changes in the histologic structure of the superficial and deep layers of the vaginal epithelium and recognized a definite intermediate cornified zone in the third and fourth weeks of the cycle In a study of serial biopsy sections taken from three normal women every third day Newton[41] observed maximum stratification and desquamation at the mid-cycle rather than at menstruation Traut and his coworkers[4] were unable to correlate changes in the superficial and intermediate layers or in the total height of the epithelium with the menstrual cycle However they did recognize cyclic changes in the basalis layer Dividing this layer into a light and a dark zone depending on the reaction to the hematoxylin stain they found a proliferation of young cells during the week before menstruation This occurred in the dark zone known as the stratum germinativum adjacent to the muscularis These proliferative changes were occasionally noted during the bleeding phase and for a few days after it

Many of the discrepancies between the findings of different observers are due to the structural variations in different parts of the vagina[15, 39]

Since biopsies taken simultaneously from different portions of the vagina often show considerable histologic variation it is readily apparent that the determination and evaluation of cyclic changes by this procedure is fraught with great difficulty

Despite the lack of agreement concerning the entire subject of cyclic histologic changes in the vaginal epithelium the pioneer studies of Papanicolaou[43] established the fact that this membrane in the human reacts to the ovarian hormonal secretions In 1933 he recorded detailed observations of smears of exfoliated vaginal epithelial cells which demonstrated conclusively the existence of a sexual cycle in the vagina of normal menstruating women This work was subsequently extended by de Allende Shorr and Hartman[44] who found a fundamental similarity between the vaginal smears of the ovulating rhesus monkey and the normal human female These workers drew a correlation between the character of the exfoliated cells and the phases of the ovarian cycle Similar correlations have been noted by Benedek and Rubenstein[4] Acknowledging the practical value of the vaginal smear as an index of ovarian hormone function it is generally agreed that correlation during the postovulatory or luteal phase is often difficult if not impossible This is in contrast to the situation in the follicular or *proliferative phase during which there is a readily demonstrable correlation* with the character of the stained vaginal smear The rising titer of estrogens during this phase causes a gradual increase in the number of cornified cells

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Chapter 19

PHYSIOLOGY OF THE OVARY

Hypophyseal Regulation, Reciprocal Relationship between the Ovary and the Pituitary. Endocrine Aspects of the Normal Ovarian Cycle. The Estrogenic Hormone: Nature, Chemistry, Metabolism, Biologic and Metabolic Actions, Levels in the Blood and Urine. The Hormone of the Corpus Luteum: Nature, Chemistry, Metabolism, Biologic Actions. Androgen Secretion by the Ovary. Physiology of Menstruation, Ovulation and Pregnancy. The Clinical Recognition of the Functioning Corpus Luteum.

By Arthur R. Sohval, M.D.

The special function of the female gonad is to provide for the reproduction of the species. This is accomplished by three closely interrelated mechanisms. Firstly, the ovaries produce ova capable of fertilization by the spermatozoon of the male. Secondly, they elaborate steroid hormones known as estrogens which maintain the accessory genitalia and the secondary sexual characteristics by which the female is distinguished from the male. Thirdly, they form the corpus luteum, a highly specialized structure which appears after ovulation and secretes the second ovarian hormone, progesterone. It is this hormonal secretion which specifically conditions the uterine mucosa for the reception and nourishment of a fertilized egg. Because of its important role in the after-care of the early embryo, the function of the ovary is necessarily more complex than that of its male homologue, the testis.

Hypophyseal Regulation. — Among the several endocrine functions of the adenohypophysis (glandular or anterior lobe of the pituitary) is one which governs gonadal activity. This is known as the gonadotropic secretory complex and in the female it dominates the production of mature eggs and hormones by the ovary. The pituitary-ovarian axis becomes established at puberty, which occurs on the average at the age of thirteen or fourteen years. This epoch marks the activation of a reciprocal relationship by which each of these endocrine glands reacts upon the other. At all times during the child-bearing span of the individual there is a constantly fluctuating, delicately sensitized balance between adenohypophyseal factors which stimulate the ovaries (gonadotropins) and the ovarian hormones. This mechanism is terminated at the menopause, which marks the cessation of ovarian function.

The Relation of the Prepuberal Ovary to the Pituitary. —In contrast to testicular function, ovarian gametogenic activity is initiated early in the prepuberal period before pituitary factors come into play. In the ovaries of the immature animal and human, growing follicles containing enlarging ova are frequently noted. Some of the follicles may even develop small

antra containing liquor folliculi Observations in the hypophysectomized rat also indicate that the early stages of oogenesis and follicle development proceed without need of anterior pituitary stimulation [1,1] Hisaw[2] calls attention to the possibility that the ovaries of very young or hypophysectomized animals may even secrete estrogen This idea is supported by the histochemical demonstration in rats by Dempsey and Bassett[3] of lipoid material in the thin theca of follicles which are not yet responsive to pituitary gonadotropins Not only is pituitary stimulation normally absent during the early postnatal period but the ovaries are actually refractory to the exogenous administration of pituitary extracts at this time Under these circumstances Hisaw postulates a self-contained system of organizers within the growing follicle capable of inducing early follicle growth Such organizers or inductor substances have been shown to be present in the embryonal gonads of certain animals by Witschi[4] Their presence is responsible for the differentiation of the early embryonic ambisexual gonad into either an ovary or a testis

Some time later in the prepuberal period of certain animals the ovarian follicles acquire a responsiveness to adenohypophyseal gonadotropic stimulation This becomes manifest spontaneously at the time of puberty but its potential can be demonstrated experimentally at a considerable interval before the actual appearance of adolescence Injections of pituitary gonadotropin into the prepuberal animal will result in premature follicle stimulation with well-defined antrum formation[5] It is probable that most mammalian species have a specific age between birth and puberty at which the young follicles acquire a sensitiveness to hypophyseal hormones[2,6] This suggests that the ovaries and the pituitary become capable of engaging in a reciprocal relationship some time before they are ordinarily called upon to do so in the natural course of events *i e* at puberty

It is not known whether this also applies to the human species since observations in the prepuberal child which would have a bearing on this subject are necessarily very limited This point could be settled along two different experimental lines One would be the ability of the gonads of a prepuberal girl to respond to stimulation by the administration of potent gonadotropic extracts The precocious appearance of evidence of ovarian function (puberal changes) would indicate a reactive capacity on the part of the ovaries Since the induction of precocious puberty is generally injudicious this type of human experimentation is neither feasible nor desirable Another line of evidence could be obtained from studies of the urinary excretion of gonadotropins by the prepuberal child in the presence of reduced ovarian function such as occurs in ovarian agenesis or castration In the mature subject the adenohypophysis responds with a markedly increased gonadotropic activity which is detectable by urinary assay Because of the rarity of this type of clinical material in the preadolescent little or no information has been gained from such studies While female[7] and male[8,1] children in the earliest stages of puberty show the adult type of pituitary response to reduced gonadal function it is unlikely that the definitely prepuberal hypophysis is capable of so reacting A single instance recorded by Heller[9] suggests that at least in the very young girl the ovary pituitary axis is impotent The case of a four year old child is cited in

whom urinary gonadotropins were low both before and for three years after oophorectomy.

There is some evidence pointing to a morphologic basis for the acquisition by the ovarian follicles of competence to engage in a relationship with the pituitary. The acquirement of sensitivity appears to coincide with the time at which the cells of the theca interna normally begin to differentiate into epithelioid structures.

The Postadolescent Ovary.—With the advent of puberty the control of follicle development and ovarian function passes into the sphere of pituitary domination. At this time the adenohypophysis begins to elaborate stimulating principles having a specific effect on the gonads of both sexes. They are known as gonadotropins and have been identified and quantitated in the human hypophysis by Witschi and Riley.[10] It should be emphasized, however, that the hormonal content of the gland does not necessarily reflect the rate or amount of its secretion. *The pituitary of the female secretes the same gonadotropins as does the male.*[11] They are three in number and have been named according to their influences on the ovary. The follicle-stimulating hormone (FSH), also known as thylakentrin,[14] produces *enlargement of the follicle largely through an accumulation of fluid* in its antral cavity. The luteinizing hormone (LH) acts on the theca interna and is responsible for its maintenance and maturation resulting in luteinization. Because of its ability to maintain or repair the interstitial tissue of hypophysectomized animals, this principle is also known as the interstitial cell-stimulating hormone (ICSH)[11] and metakentrin.[13] The third gonadotropin maintains the activity of the corpus luteum once it is formed and hence is called the *luteotropic hormone*. It is identical with the lactogenic hormone, prolactin, which influences the secretory activity of the breasts.

The great importance of the regulatory influence of the adenohypophysis *on the ovaries is well demonstrated in hypophysectomized animals*. The specific manner in which hypophyseal gonadotropins influence ovarian structure and function has been amply but by no means completely elucidated by further studies in the immature animal subjected to pituitary *stimulation*.

The pioneer experiments of P. E. Smith[17, 18, 19] showed that hypophysectomy results in atrophy of the gonads which can be reversed by daily implants of pituitary tissue. He also demonstrated that precocious puberty *could be induced in healthy immature animals by similar pituitary grafts*.[20, 21] These experimental findings were preceded by the clinical observations of Cushing and Goetsch, who found that gonadal atrophy follows human pituitary insufficiency. The early observations of Smith and Smith and Engle[3] *for the rat and mouse have been confirmed in many species*.

Following ablation of the pituitary in the immature female a certain amount of oogenesis and follicular development proceed. However, none of the follicles mature or become luteinized, while many become atretic. The *interstitial tissue remains undeveloped and the sex accessories* (uterus and vagina) continue in the infantile state, indicating little, if any, ovarian secretory function.

In the adult animal hypophysectomy causes retrogressive changes in the ovaries and accessory genitalia.[4] The smaller follicles remain intact while the large vesicular Graafian follicles degenerate and undergo atresia. Maturation and ovulation of the follicles does not occur and eventually many of the smaller vesicular follicles undergo atresia without luteinization.[12] Pre-existing corpora lutea become non-functional and gradually involute. The uterine and vaginal structures return to an infantile state, indicating a sharp reduction of ovarian secretory function.

Although it had been shown earlier that pituitary substance was capable of preventing and repairing ovarian regression after hypophysectomy, it was not until recently that the specific effects of the individual gonadotropic principles could be clearly demonstrated. This came about after prolonged and laborious efforts to fractionate and isolate the separate gonadotropins in pure form. Purified LH was prepared almost simultaneously in three different laboratories in 1942 and 1943 by Chow, van Dyke and Greep,[45] Li, Simpson and Evans,[6] and Fevold.[7] Pure FSH was successfully obtained at about the same time by Chow.[28] Following the earlier demonstration of an adenohypophyseal lactogenic principle by Riddle and Braucher in 1931,[77] it was shown by Evans and his collaborators in 1941[78] that the lactogenic hormone (prolactin) also controls the functional activity of the corpus luteum. This and other observations established the existence of a third pituitary gonadotropin which accordingly is known as the luteotropic principle.[49] Burrows[15] points out that the presence of a pituitary hormone having effects on two widely separated target organs (breast and ovary) was first suggested by Desclin and Gregoire.[16] These workers noted that luteinization occurs in ovaries which have been grafted into spayed mice provided that they are suckling at the time.

Despite extensive investigation, many gaps still exist in our knowledge concerning the specific manner in which gonadotropins influence the ovaries and synergize with one another. Broadly speaking, it may be stated that the follicle-stimulating hormone promotes the development of the ovarian follicle and its contained ovum, presumably by action on the granulosa cells. The production of estrogen requires the simultaneous effect of the luteinizing hormone. The influence of the latter is principally on the theca interna cells and its action has a two-fold effect. One is the production of estrogen by synergism with FSH. This same synergistic action is also ultimately responsible for ovulation. The other effect is the luteinization of the theca and granulosa cells of the follicle. This process is essential for the elaboration of progesterone which subsequently occurs under the influence of luteotropin.

In general, the actions of the pituitary gonadotropins in the female are analogous to those in the male. FSH influences follicle and ovum growth in the ovary and spermatogenesis in the testis. LH (or ICSH) is necessary for estrogen production, final follicle ripening, ovulation and transformation into corpora lutea in the ovary, while it stimulates the testicular Leydig cells to elaborate androgenic hormone. An important sex difference lies in the ability of LH to stimulate hormone production in the testis without the aid of FSH. This is not true for the ovary where the synergistic action of both LH and FSH are required for estrogen secretion. These functional dif-

ferences are probably related to the absence of strict morphologic homologies between the anatomic substrates in the male and female gonad.

The Reciprocal Relationship Between the Ovary and the Adenohypophysis. — Additional data bearing on ovary-pituitary interrelationships are available from experimental studies dealing with castration on the one hand and the administration of estrogens to the intact organism on the other. These indicate that the relationship of the pituitary to the ovary is not exclusively unidirectional in that the female gonad, like the male, exerts a counter-effect on the pituitary.

Removal of the ovaries deprives the subject of its gametogenic and sex endocrine functions. In addition to sterility two phenomena occur as a result of ovarian hormonal failure. One is the involution of the sex accessories and the cessation of cyclic changes therein. The other is the release of the adenohypophysis from estrogenic inhibition resulting in an excessive elaboration and secretion of gonadotropic hormone predominantly of the FSH type. Many of the effects due to hormonal deprivation can be prevented or repaired by the administration of estrogenic hormone.

Evidence for the effect of ovariectomy on the pituitary dates back to 1905. Fichera[34] showed that gonadectomy in either sex of several experimental animals resulted in enlargement of the pituitary associated with characteristic histologic changes. That increased pituitary weight after gonadectomy in female and male rats is correlated with augmented gonadotropic potency was demonstrated by Evans and Simpson.[35] The increase is almost entirely of the FSH principle with some reduction of LH. Similar results have been obtained with ovariectomy in immature rats nineteen to thirty days old.[36] Hypergonadotropic pituitary activity in the human was reported by Zondek[37] who found an increased urinary excretion of FSH in women shortly after bilateral ovariectomy. The question of how early in life the adenohypophysis develops the capacity to secrete excessive quantities of gonadotropins as a result of reduced gonadal function has not been settled. This phenomenon has been observed during *early* adolescence in children of both sexes. Wilkins[7] reports an increased urinary excretion of pituitary gonadotropins in a girl of twelve years and ten months of age whose gonadal insufficiency was due to ovarian agenesis. A similar pituitary response promptly following orchidectomy has been noted by Hamburger[71] in a boy of twelve years of age and by Hamilton and his coworkers[8] in 3 boys aged thirteen, fourteen and fifteen years. Observations in the very young prepuberal child are extremely scarce. A case cited by Heller[8] is pertinent. The urinary gonadotropins of a four year old girl were low before and for three years after ovariectomy. While there is evidence that the ovary-pituitary axis becomes capable of functioning in both sexes during the earliest stages of puberty, it is highly improbable that this can occur before the age of eleven or twelve years.

Conversely, estrogenic hormone has both a stimulating and a depressing effect upon adenohypophyseal gonadotropic activity depending upon the dosage employed. Frank[33] reported low doses to be stimulating and large doses to be suppressing. In adult rats Lane and Hisaw[33] found an increased output of LH as an early effect of estrogen administration. Marked inhibition of pituitary gonadotropic activity by the administration

of large doses of estrogens has been amply demonstrated in the experimental animal of both sexes by Nelson[29] and by Moore and Price.[44] In castrated women Frank and Salmon[10] caused the urinary excretion of excessive amounts of pituitary gonadotropin to disappear with estrogen therapy. Synthetic and natural estrogens react on the pituitary in the same manner.

Progesterone, the specific hormone of the corpus luteum, shares with estrogens and androgens an inhibitory effect on pituitary gonadotropic activity. It is well known, for example, that a persistent corpus luteum inhibits follicle development in the ovary. Furthermore, ovulation can also be inhibited or delayed by the administration of progesterone. However, Fevold[45] believes that the inhibitory effect is primarily upon the LH rather than the FSH output of the adenohypophysis, and he summarizes the available evidence in support of this contention.

From the foregoing brief summary of experimental evidence, it is clear that the gonadotropic activity of the adenohypophysis is sensitive to the amount of circulating ovarian hormones, principally estrogens. This is true to a considerably lesser degree for androgens, large doses of which are also known to depress pituitary gonadotropic activity in the female[41] as well as the male.[42, 43, 44] Under physiologic conditions, as well as in pathologic states involving the ovaries or their hormones, a delicate mechanism exists whereby the gonadotropic activity of the adenohypophysis is held in check by the estrogenic hormone and to a lesser extent by progesterone. This provides a mechanism of interglandular balance the object of which is to maintain optimal hormonal concentrations and glandular function at all times.

Endocrine Aspects of the Normal Ovarian Cycle.—It may be stated categorically that both FSH and LH are essential to normal follicle development and ovarian secretory function. There is evidence that the estrogenic hormone elaborated as a result of adenohypophyseal gonadotropic stimulation is likewise indispensable for complete follicle development. Williams[2, 30] has shown that the administration of estrogens to rats two days after hypophysectomy is capable of preventing ovarian atrophy. This maintaining effect of the ovary's intrinsic secretion on its follicular structure is comparable to the ability of testosterone to maintain tubular integrity in the male rat when administered soon after hypophysectomy.[31, 3]

The role of the pituitary gonadotropins in the evolution of the Graafian follicle, ovulation and the formation of the corpus luteum begins at puberty. Throughout reproductive life there is a constant shift in the ratio of the amount of FSH to the amount of LH secreted by the adenohypophysis. The fluctuations in the FSH-LH ratio are cyclic and correspond to the cyclic rhythm of ovarian follicle maturation. With the termination of ovarian activity by natural or induced menopause the gonadotropic activity of the anterior lobe of the pituitary increases sharply with a predominant output of FSH.

In Allen's[1] opinion, estrogen from partly developing follicles initiates cyclic sexual activity at the approach of puberty. In response to slowly rising levels of estrogenic hormone, the adenohypophysis is stimulated to secrete FSH. Higher levels subsequently depress FSH secretion while at the same time they promote the secretion of LH. It is hardly to be ex-

pected that the pituitary-ovary axis would attain an optimal efficiency at its inception or that the first menstrual flow would be preceded by ovulation. Observations by Hartman[86] in the rhesus monkey indicate that the assumption of effective reproductive activity by the ovary occurs only after a series of staircase phenomena requiring a period of at least a year. He showed that after any amenorrheic interval including pregnancy and the non-breeding season there is a time-consuming transition during which the ovary approaches maturity *in ascending step-like fashion*. *Periodic* bleeding in the monkey is noted before growth of the ovary and the *uterus can be detected*. *Some time after the periodicity of the latter has* been established in a similar staircase fashion the ovary finally ovulates and the subject is ready *for reproduction*. Since *comparable studies in the* pubertal girl are lacking, it cannot be definitely stated that a similar mechanism exists *in the human*. However, in view of the close similarity between reproductive phenomena in the rhesus monkey and the human this possibility is not unlikely. Such a supposition gains strength from the frequency with which irregular uterine bleeding and sterility are encountered for some time after the menarche.[233]

Once established the ovarian cycles are repeated in orderly fashion, although each cycle is not necessarily accompanied by ovulation.[56] The periodicity of the sexual function continues throughout reproductive life unless modified by pregnancy or disease.

From the available experimental and clinical data it is possible to epitomize the endocrine relationships which transpire during the completion of an ovarian cycle. As previously emphasized, not all the lines of evidence are final or continuous so that many items are still within the confines of speculation. Since the ovarian and menstrual cycles are synchronous, it is customary to date the beginning of a new ovarian cycle from the first day of the menstrual flow. At the beginning of the cycle relatively small amounts of estrogen are available as a result of the decline of the premenstrual corpus luteum. As a group of new *follicles* enlarge in competition to become the favored follicle, there results an increased estrogenic secretion. *First the presence of relatively low quantities of estrogens, then* their increasing levels evoke an increased FSH output by the adenohypophysis. *By this time one follicle has been singled out as the* favored follicle and comes to stand upon the shoulders of its contemporaries.[1] Its function is said to be supported by that of its satellites and it undergoes stimulation by FSH. The latter causes further enlargement of the follicle which soon develops an antrum filled with fluid. The precise cellular constituents upon which FSH acts are not known although these are generally thought to be the granulosa cells. Furthermore, the source of the fluid has not been established. This is the limit of FSH action in the hypophysectomized rat and estrogen secretion and further maturation of the follicle fail to occur in the absence of LH.

Presumably during the second week of the cycle increasing concentrations of LH become effective. The specific action of this principle is on the theca interna which it causes to mature. By the synergistic action of FSH and LH *estrogenic hormone appears in the follicular fluid*[16] *and* the level in the blood is accordingly increased. Estrogen is apparently formed by the

theca cells.[54] It is not known whether the granulosa cells share in the production of estrogen or whether estrogen plays a role in the growth and differentiation of the granulosa.[2] Allen[47] is of the opinion that estrogen may be secreted by *all* of the ovarian epithelial cells (granulosal, thecal, luteal and interstitial cells). The rising titer of estrogen reacts back on the adenohypophysis to cause a shift in the FSH:LH ratio in favor of the latter. This occurs toward the end of the first half of the cycle when there is a rapid growth in the size of the follicle due to an increased accumulation of liquor folliculi (pre-ovulatory spurt).

Ovulation usually occurs at about the middle of the cycle, although there is a good deal of variation in the timing of this event. The exact mechanisms underlying the causes of ovulation are not known, but here again observations in the experimental animal indicate that a proper balance of FSH and LH are essential for the discharge of the ovum. The balance in this instance is probably largely in favor of LH.[2]

Following ovulation the follicle is converted into the corpus luteum. The same cells which formerly secreted only estrogen now secrete progesterone in addition. Since lutein changes have been recognized in the walls of ripe follicles just before ovulation in some animals, it is possible that progesterone secretion may be initiated at the same time.[47,48] With the discharge of the ovum and some of the follicular fluid there is a slight but temporary drop in the level of circulating estrogens. As the corpus luteum approaches maturity with conversion of its granulosa and theca cells into lutein cells, there is a secondary rise in estrogenic output, now in association with a gradually increasing secretion of progesterone. The activity of the corpus luteum and its hormonal secretion are under the influence of the third adenohypophyseal gonadotropin, luteotropin.[49] There is convincing evidence that while LH stimulates the formation of luteal tissue, it is not responsible for the function of this tissue or the secretion of progesterone.

The height of corpus luteum activity is attained about one week after ovulation or approximately the twenty-first day of a twenty-eight day cycle. Back action on the hypophysis again occurs resulting in decreased gonadotropic activity. With the secretion of estrogen and progesterone at a peak, the uterine mucosa has also attained a maximum degree of development in preparation for nidation of a fertilized ovum. If fertilization and implantation of an ovum occurs, the corpus luteum maintains its activity for about three months under the influence of chorionic gonadotropin, a placental hormone. During this time no new follicles mature. On the other hand, in the absence of conception the corpus luteum begins to involute soon after reaching its peak. According to Brewer[72] this occurs in the human on about the twenty-second or twenty-third day of the cycle, while Corner[73] believes it to occur some time later on about the twenty-fifth or twenty-sixth day. This process of retrogression causes a decline in the circulating levels of estrogen and progesterone. Markee[50,51,52,53] has shown in the brilliant experiments alluded to in the previous chapter that it is the *sudden* withdrawal of the ovarian hormones that is responsible for the initiation of menstruation. Profound alterations in the endometrial vasculature appear to be the precipitating cause. It is not known how a reduction of hormones

mediates these changes. The current theories concerning the mechanisms involved in menstruation are discussed in a later section.

While the previous corpus luteum progresses to involution the menstrual period already marks the beginning of a new sexual cycle in one or the other ovary. The above-described process of follicle development continues to be repeated with each new menses.

Anovulatory Cycles.—It has been mentioned previously that the vast majority of ovarian follicles degenerate before attaining any significant degree of growth. This applies principally to primitive follicles of which a few hundred thousand are present in each ovary at birth. With each fruitful ovarian cycle there are several satellite follicles which undergo partial enlargement and then fall by the wayside to become atretic. In a broad sense, these may be referred to as passing through an anovulatory cycle. However, within the strict meaning of the term, this expression is reserved for those ovarian follicles which are selected, one at a time, to become the "favored follicle" of a sexual cycle. Its destiny differs from that of the typical Graafian follicle in that its contained ovum is not discharged. A further important difference lies in the absence of corpus luteum development. After a variable length of time, often within a four-week period, follicular activity begins to wane as the follicle undergoes atresia. This type of follicle cycle is occasionally encountered during the child-bearing span, although its exact frequency is unknown. It is more apt to occur at the time of the menarche and at the climacteric. It is a normal phenomenon in the rhesus monkey during the summer non-breeding months.[65]

The mechanisms underlying the failure of an active, estrogen-secreting Graafian follicle to ovulate are not well understood. The fact that estrogen is being secreted (as gauged by its effect on the endometrium and vaginal smears) is evidence that FSH and LH are at least present even if not in the proper ratio. From an endocrinologic point of view, the anovulatory cycle differs significantly from the previously described cycles which are characterized by ovulation. The absence of a corpus luteum means that progesterone secretion does not occur in appreciable amounts. Nevertheless, such anovulatory cycles are often accompanied by periodic uterine bleeding which is indistinguishable from true ovulatory menstruation. According to Markee[50,51,52,53] the sudden withdrawal of estrogenic hormone as a result of atresia of the follicle results in the same endometrial vascular changes which are encountered in ovulatory menstruation. Hence he believes the mechanism for the bleeding to be the same irrespective of whether ovulation had occurred.

THE HORMONES OF THE OVARY

By its internal secretions, the ovary has a dominant influence over the growth and development of the accessory genitalia as well as the secondary sexual characteristics. It is also responsible for the progestational proliferation of the endometrium which enables the embryo to grow after it has been implanted. These two functions are distinct in that the former can exist without the latter. However, the progravid function is completely

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THE HORMONES OF THE OVARY

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dependent upon the adequacy of the first or estrogenic function. The normally functioning ovary therefore elaborates two hormones which are entirely separate though often complementary. The first is the hormone of the Graafian follicle, *the estrogenic hormone.* The second is the hormone of the corpus luteum, progesterone. In addition there is evidence that the ovary may secrete an androgenic hormone.

The Estrogenic Hormone.—*The principal hormone of the ovary is known as the estrogenic hormone* because of its ability to induce vaginal cornification identical with that of natural estrus. All substances which possess this quality *are therefore known as estrogens.* The correlation between estrous changes in the vagina and cyclic changes in the ovarian follicles was first established in 1917 by Stockard and Papanicolaou[57] in the guinea pig. These studies were soon *confirmed in other laboratory animals*[58,59] and pointed to the Graafian follicle as the source of the hormone.

Nature and Identification.—Although it was long known that sexual function in the female is dependent upon the ovaries, *it was not until 1896* that observations were recorded which served as a basis for the concept of an ovarian hormone. This was almost fifty years after transplantation experiments demonstrated a corresponding *testicular hormonal mechanism* in the male animal.[69] Knauer[60] showed that ovarian grafts in the dog would prevent atrophy of the uterus after castration. These studies were extended[61] and confirmed by *Halban*[70] *who demonstrated that ovariectomized* immature guinea pigs develop normal puberal changes when implanted with ovarian grafts. In 1905 Marshall and Jolly[6] contributed the important *information that the injection of extracts of ovaries removed from a* dog during estrus or implantation of estral ovaries induces estrus in the castrated bitch. These workers also found that the secretion which produces estrus *is different from another formed by the corpus luteum.* Thus they recognized the existence of two different hormones.

A most significant advance in the identification of the estrus-inducing *ovarian hormone came with the observations of Allen and Doisy*[63] *in 1923.* Injection of fluid aspirated from sow's ovarian follicles was found to induce vaginal estrous changes in ovariectomized rats and mice. An estrogenic substance was *first identified in humans in 1925* by Frank and his co-workers[64] and Loewe.[65] Small amounts were detected in the menstrual and peripheral blood. In 1927 Aschheim and Zondek[66] demonstrated *the presence of estrogenic substances in the urine of pregnant women.*

Isolation of a crystalline estrogenic hormone from human pregnancy urine was accomplished in 1929 by Doisy, Veler and Thayer[67] and by Butenandt.[68] This was the *first* estrogen to be identified chemically and proved to be estrone. These investigations marked the beginning of extensive research into the nature, identification, *chemistry and metabolism* of the estrogenic hormones. The second estrogenic hormone to be isolated and identified chemically was estriol. Browne[74] recovered it in pure form from the human placenta in 1930. *A third estrogenic hormone, α-estradiol* was demonstrated in 1936 by MacCorquodale, Thayer and Doisy.[75] These workers isolated this substance from the liquor folliculi of sows' *ovaries. It proved to possess the greatest estrogenic* activity of all three hormones and is now believed to be the principal hormone secreted by the

Graafian follicle. It has not as yet been identified in the human ovarian follicle.

These epochal chemical achievements established the fact that the estrogenic hormones in man are really three in number and led to a clarification of the meaning of the term *estrogen*. Originally it was applied to the follicular hormone which had been demonstrated to be able to produce estrous changes in the vagina of the immature or castrated animal. It was therefore known as "folliculin," "estrin," or "theelin." After the isolation of three different substances having estrogenic activity, each with a known chemical structure, the individual hormones are now known by names derived from their chemical composition. Estradiol is so named because it contains two "ol" (hydroxyl) radicals. Estriol obtained its name because of its three hydroxyl groups. Estrone drew its name from the fact that it contains a ketone substituent. All three hormones are found in the urine of women during their child-bearing span of life. Each can be synthesized in the laboratory and they differ markedly in their estrogenic potency.

With the exception of estriol which is specific for the human species, the estrogens found in human urine are also found in the urine of stallions[6, 7] and pregnant mares.[78, 9] Of considerable interest is the fact that five other estrogenic steroids have been isolated from the urine of pregnant mares. These include equilin and its isomer hippulin,[80] equilenin,[81] β-estradiol[illegible] and β-17-dihydroequilenin[82] (β-follicular hormone?). These serve to potentiate the activity of estrogenic compounds prepared from this source. The equine estrogens differ from the human compounds chiefly by virtue of their unsaturation in ring B. They have been found useful in devising methods for the chemical synthesis of estrone.

In addition to the naturally occurring estrogens described above, several compounds having a non-steroidal composition but a marked estrogenic potency have been prepared in the laboratory. In 1937 Dodds and Lawson[107] synthesized a stilbene derivative, diethylstilbestrol, which was found to be as potent an estrogen as α-estradiol and, more important, it was effective on oral administration. Other artificial estrogens such as hexestrol,[124] dienestrol,[125] benzestrol[126] and triphenylethylene[127] were then prepared.

Origin of Estrogens.—The chief sources of estrogens in the human are the ovaries and the placenta. The adrenals produce a much smaller amount. The testes of certain animals also elaborate estrogens. This is particularly true of the stallion whose testes[84] and urine[7] may contain very large quantities. The possibility of an estrogenic secretion by the human testis has been discussed at length in a previous section.

The discovery of the estrogenic activity of follicular fluid[83] and its subsequent identification as α-estradiol[75] pointed to the ovarian follicle as the source of the estrogen. It was first thought that the granulosa cells are responsible for its elaboration but this supposition has been discarded by most workers in view of the results of animal experiments in which ovarian follicular cells were destroyed by roentgen irradiation.[86, 87, 88] The preservation of estrogen effects, as indicated by continued maintenance of the accessory genitalia, is taken as evidence that other cells are at least a more

important site of secretory function Although Allen[87] believes that all the ovarian epithelial cells (granulosal thecal luteal and interstitial cells) may secrete estrogen there is no proof that granulosa cells are a source of estrogen Since there is no evidence in the human of cortical interstitial cells having a secretory function the production of estrogen is generally believed to originate in the cells of the theca interna Aschheim,[85] Corner[84] [3] and Dempsey and Bassett[3] are of this opinion The last named workers found histochemical evidence of steroid secretion in the cells of the theca interna and not in the granulosa layer

To Fellner[89] belongs credit for the discovery of the placenta as an important source of estrogenic activity Subsequently, estriol[4], estrone[90] and α-estradiol[91] were isolated from human placental extracts Of the three estrogens estriol is excreted in the urine of pregnant women in the greatest quantity It was first isolated from human pregnancy urine by Butenandt and Browne[92] and has not been demonstrated in any other species

The isolation of estrogens from the placenta and their identification in the urine of pregnant women does not necessarily prove that they are elaborated by the placenta In other words the possibility of storage rather than production remains to be considered Furthermore estrogen is found in the urine of non pregnant ovariectomized women[94] and in extracts of animal hypophysis and adrenal glands[9] This indicates that it can be formed elsewhere than in the ovaries and placenta (*i e* adrenals) and that it can be demonstrated in tissues not known to produce estrogens Nevertheless considerable data of a circumstantial nature have been accumulated to indicate that the placenta actually possesses an endocrine function Estrogen is excreted in the urine of women at an increasing rate during pregnancy[111] This increased excretion continues even if ovariectomy is performed in the second or third month of pregnancy[96, 97, 111] Moreover it is excreted in amounts similar to those excreted by the normal pregnant woman near term[97] Parturition with passage of the placenta is followed by a rapid decline in the urinary excretion of estrogens[98] Although not conclusive the available evidence suggests that the placenta is the site of significant estrogen production Observations in certain mammals indicate that both the fetal and maternal components of the placenta contain estrogen[93] It is not known whether this applies to the human

The adrenal cortex is another source of estrogens Substances possessing estrogenic activity have been isolated from the adrenal glands of animals[9, 99, 100] and human fetuses and newborn babies[101] The recovery of estrogen from the urine of ovariectomized women[94] has been previously mentioned its origin being presumably from the adrenal Large amounts of estrogens have been found in the urine of women[102, 19] and men[103, 0] with adrenal cancer suggesting that hyperfunctioning adrenal tissue may be the source of excessive estrogen formation A related phenomenon is observed in certain strains of mice where ovariectomy results in the formation of adrenal hyperplasia and tumor associated with increased estrogen elaboration[104, 105, 106]

It is thus apparent that several different natural estrogens have been obtained from various sources These are listed in Table 23 which includes the organs from which they have been isolated and in which they are pre-

sumably synthesized. A single reservation in this connection concerns estrone and its presence in the sow's ovary. Pearlman[109] points out that it has been demonstrated in the swine ovary[110] but has not been isolated therefrom. Also tabulated are the various urinary sources from which natural estrogens have been recovered. Although estrogenic substances are present in both male[109] and nonpregnant female urine the quantity is very small and fractionation into the individual compounds is extremely difficult. During pregnancy the excreted amount is large enough to permit quantitative partition. Estrogens are excreted in two forms: a smaller amount in the free state which is biologically active and a larger quantity in the conjugated form which is inert until subjected to acid hydrolysis. A large proportion of free estrogen is present in the urine of pregnant women for about one week prior to parturition.[170] Estrogens are conjugated in the organism with sulphuric and glucuronic acid and the combined form are excreted principally as estrone sulphate and estriol glucuronide.

TABLE 23.—NATURAL ESTROGENS AND THEIR SOURCES

Estrogen	*Likely organs of synthesis*	*Urinary sources*
Estrone	ovary of swine	
	placenta of human	human pregnancy
	adrenal of animals	
	testis of stallion	stallion
		mare pregnancy
		human male
Estrone sulphate		*mare pregnancy*
α-estradiol	ovary of swine	
	placenta of human	human pregnancy
	testis of stallion	stallion
		mare pregnancy
Estriol	placenta of human	human pregnancy
Estriol glucuronide		human pregnancy
Equilin		mare pregnancy
Hippulin		mare pregnancy
Equilenin		mare pregnancy
β-estradiol		mare pregnancy
β-dihydroequilenin		*mare pregnancy*

The precise nature of the estrogenic hormone secreted by the human ovary is unknown. Since α-estradiol has the greatest estrogenic activity it is regarded as the principal if not the only follicular hormone. Several known facts support this hypothesis. It is the only estrogenic hormone to be isolated in crystalline form from ovarian tissue. It is apparently absent from or occasionally present in minute amounts in the urine of normal nonpregnant women, a fact consistent with metabolic conversion of a parent hormone. The presence of estrone and estriol in the urine of subjects following the administration of α-estradiol[109] suggests that these are probably products of metabolic degradation. This is compatible with the failure to isolate these hormones from ovaries. The presence of all three estrogenic compounds in pregnancy urine does not invalidate the supposition that

α-estradiol is the true parent follicular hormone. During pregnancy large amounts of the individual hormonal substances, especially estriol, are presumably elaborated by the placenta.

Chemical Structure and Relationships of Estrogens. — The estrogens (and progesterone) in common with the steroid hormones of the adrenal cortex and testis have a basic structure known as the perhydrocyclopentenophenanthrene nucleus. It consists of the fully saturated (perhydro) three benzene phenanthrene ring to which a five-carbon ring (penteno) is attached. The rings are successively labelled A, B, C and D and each carbon atom is numbered to indicate the position of substituents and double bonds.

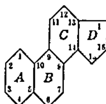


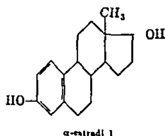
Fig. 51. — The basic perhydrocyclopentenophenanthrene nucleus.

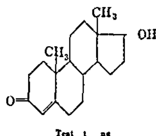
Significant alterations in the biologic activity of the compound are produced by relatively minor substitutions or additions at the different carbon positions. The presence of double bonds also affects the potency and nature of the various substances. In addition, stereoisomerism, by which chemically identical compounds differ only in the spatial relationships of a radical, usually has a marked effect on biologic activity. In general the estrogens differ from androgens in having a greater degree of unsaturation and one less methyl group. This is attached to the 13th carbon atom, while androgens have a methyl group at both the 13th and 10th carbon positions. Curiously enough, the structure of the second ovarian hormone, progesterone, is more closely allied to that of the androgens and the adrenocortical hormones than it is to the estrogens. Its two angular methyl groups and single double bond in ring A relate it to the androgenic series, while a two carbon side-chain at the 17th carbon position produces a close resemblance to the steroid hormones of the adrenal cortex. The structural relationships between the various steroid hormones is set forth in figure 52.

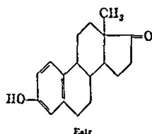
Since stereoisomerism involves three dimensions in space, it was found necessary to adopt a system of depicting the geometric isomers on a plane surface.[121, 122] These are distinguished by the indices α- and β, the α configuration being shown with a dotted line and regarded as below the plane of the ring concerned. The β configuration is represented as a solid line denoting a position above the plane of the ring. These designations apply principally to the 3 and 17 carbon positions and concern hydroxyl (HO–) but not carbonyl (C =O) groups. The single valency bond of the former permits two alternate positions in space while the double bond of the latter maintains a fixed position. The methyl groups attached at the tenth and thirteenth carbon positions are called "angular" because of their situation in the angle formed by adjacent rings. An excellent review

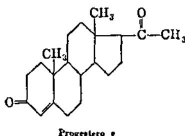
of the nomenclature of the steroid hormones and their derivatives has been presented recently by Mason [1 2]

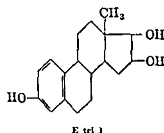
As previously mentioned α-estradiol is the most potent natural estrogen and is believed to be the hormone secreted by the ovary It differs from estrone only in having a hydroxyl group instead of a ketone group at the seventeenth carbon position Its stereoisomer β-estradiol * is present in mare's urine [82] It possesses very little estrogenic activity and is not en











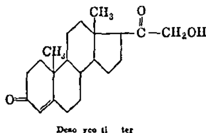


Fig 52 —Structural formulas of the human estrogens showing their relationship to progesterone and the steroids of the testis and adrenal cortex

The effects of stereoisomerism at the 17th position are not as clear as those of the 3rd carbon atom Alpha-estradiol was so-named originally because its 17 OH group was regarded to be below the plane surface of the steroid nucleus However Miescher[133] points out that this group is probably above the plane of the ring since it appears to be in the *cis position* relative to the angular C-13 methyl group In this event the 17-hydroxyl group would really be in the β-position The corresponding radical of the stereoisomer β-estradiol would therefore be in the *trans* or α-position Since the original designations have become so firmly implanted in steroid chemistry literature attempts to reverse the terminology at this time would only lead to confusion

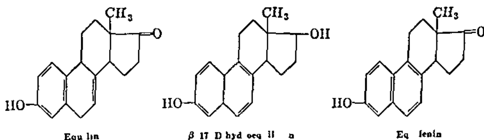
countered in normal human urine.[132] In human pregnancy urine it is absent or present in very small amounts.[1,8] In the rabbit, it appears to be a significant metabolic degradation product of administered estrone[1,8,19] and α-estradiol.[130,131]

The relative potency of the different estrogens is difficult to evaluate since estimates vary according to the method of assay and the particular test animal employed. Pearlman[109] has compiled data obtained by the vaginal response method in the spayed rat suggesting that α-estradiol is about 10 times as potent as estrone. It is about 50 times as potent as estriol and has about 100 times the estrogenic effect of β-estradiol. It must be emphasized that these figures are only rough approximations although the comparative estrogenicity for most species tested stands in the order mentioned. Esterification of estrogens results in a prolongation of their effects,[34] an observation which has been utilized clinically in estrogen therapy. Estrogen esters of benzoic and propionic acid are the ones one most commonly employed.

The estrogens, like the androgens in the urine, are present principally as water-soluble, biologically inactive, conjugated compounds. These substances must be subjected to acid hydrolysis in order to free the water insoluble, fat soluble, biologically active estrogens.

The estrogens present in mare's urine are of considerable interest from two points of view. Firstly, they provide a rich source of estrogenic substances. Secondly, those estrogens which are peculiar to the equine species are of value in understanding and developing synthetic procedures involving steroidal compounds. In addition to α-estradiol and estrone, the pregnant horse excretes five estrogenic compounds. These are equilin, its isomer hippulin,[60] equilenin,[81] β-estradiol[5] and β 17-dihydroequilenin.[63] The last named compound is also known as δ follicular hormone.

The equine estrogens differ from those of the human principally in the unsaturated state of ring B. The structure of some of these compounds is as follows:

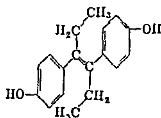


Equilin β 17 Dihydroequilenin Equilenin

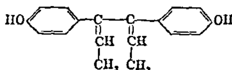
The synthesis of artificial non-steroidal compounds possessing estrogenic activity was initiated by Dobbs and Lawson[107] with the preparation of diethylstilbestrol. The structural composition of these substances is presented in figure 53. A resemblance to the four ring structure of the pentenophenanthrene nucleus is apparent if one regards rings B and C as having been opened and an enlarged ring D as having been aromatized. These compounds possess a high degree of estrogenic activity, diethyl

stilbestrol being of the same approximate order as α-estradiol.[134] In contrast to the natural estrogens they are very effective upon oral administration, a fact which markedly increases their clinical usefulness.

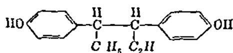
Metabolism of the Estrogens.—Our knowledge of the metabolism of estrogens is fragmentary and inadequate. This is due largely to the minute amounts that occur normally in the blood and urine and to the lack of accurate methods of quantitative assay.



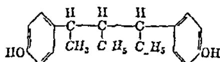
Diethylstilbestrol



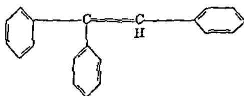
Dienestrol



Hexestrol



Benzestrol



Triphenylethylene

FIG. 53.—Structural formulas of some artificial non-steroidal estrogens.

The anabolic processes concerned in the synthesis of estrogens within the organism are imperfectly understood. Cholesterol is regarded as an estrogen precursor and certain observations tend to support this hypothesis. The cyclopentenophenanthrene nucleus is common to both cholesterol and the estrogens. It is also found in adrenocortical and testicular steroid hormones. A correlation between adrenocortical function and cholesterol (and ascorbic acid) content of the adrenal has been established by Long[112] and by Sayers and Sayers.[113] Although no such correlation could be demonstrated for the secretory function of the testis,[114, 115] it appears from the observations of Everett[116] and Claesson and Hillarp[117, 118] that ovarian function may be related to the cholesterol content of the ovary. This is con-

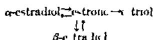
gens from the circulation with a speed which varies with the conditions of the experiment and the species of animal employed. Data derived from observations of Szego and Roberts[151,152,153,154] suggest a further hepatic role in estrogen metabolism. From a series of studies concerning the nature of circulating estrogens these workers believe that there is an equilibrium between physiologically inactive protein bound estrogens and active estrogens in the form of a conjugate. About two-thirds of the circulating estrogen is believed to be bound to protein. This serves as a readily available source of active estrogen as the latter is removed by the tissues. It is postulated that the liver functions in the formation of this protein-complex and that therefore the liver is essential for estrogen activity. At the same time the liver appears to prevent active estrogens from reaching the systemic circulation in large amounts.

The role of vitamin B complex in hepatic function with respect to estrogen inactivation has been extensively studied. There are many observations which illustrate the inability of vitamin B-deficient animals to inactivate estrogens.[155,156,157] In accordance with these observations attempts have been made to relate clinical states allegedly due to hyperestrinism to decreased estrogen inactivation by a vitamin B deficient liver.[158] These claims and results with vitamin B therapy have not been confirmed. Furthermore it has now been definitely established that the effect of acute vitamin B complex deficiency on hepatic inactivation of estrogens is due to concomitant inanition.[189,190] Nevertheless the probable enzymatic nature of hepatic estrogen inactivation and the fact that the B vitamins serve as coenzymes suggest that thiamine and riboflavine may play a definite role in estrogen metabolism.[296]

In connection with the relation of vitamin B complex to estrogen metabolism attention is drawn to recent observations[191,192,193] indicating the importance of one of the B vitamins, folic acid. This substance appears to be required to enable the genital tissues of chicks and monkeys to respond to estrogens. Its effect is presumed to be operative at the end-organ level possibly through an enzyme system and not in the liver. The importance of folic acid in estrogen activity is further emphasized by experiments involving the use of folic acid antagonists.[194,195] These substances act as antivitamins and their administration interferes with the utilization of the folic acid vitamin. The ingestion of the folic acid antagonists sharply reduces the typical response to estrogens.

Recent observations by the Fishmans[196,197] suggest that a specific enzyme mechanism may play a vital role in the utilization of estrogens by the end organs. These workers studied the activity of β glucuronidase, an enzyme believed capable of catalyzing the synthesis *in vivo* of conjugated glucuronides. They found a greatly increased activity of this enzyme in the uterus of mice in response to exogenous estrogens. This increased activity was not noted in any of the other organs examined. The experimental findings suggest that conjugation of estrogens (glucuronide formation) within the target organ is an important process in the utilization of these hormones. This would represent, according to the above authors, a metabolic conjugation, in distinction to the detoxifying and inactivating effect of conjugation which occurs in the liver.

While many gaps exist in our knowledge of estrogen metabolism certain facts are known concerning intermediary stages Like testosterone estradiol is converted in the human organism into degradation products of lesser biologic potency The best known of these compounds are estrone and estriol [34] The results of numerous studies in animals and humans dealing with the detection of estrogen metabolites after the administration of large doses suggest the following metabolic pathways [109]



β-estradiol does not participate in the metabolic process in normal humans It is included as an example of the differences encountered in various species Whereas estrone can be converted to α-estradiol and estriol in man and most animals the formation of β-estradiol occurs after its administration in the rabbit Estriol has been isolated only from human material

The great proportion of injected estrogen is apparently inactivated in the organism Jailer[162] has reviewed the literature and finds that only a very small amount (less than 5 per cent) of injected estrogen can be recovered in the urine [129 131 137 163 164 165 166 167 168] A similar amount has been recovered from the feces [169] The fecal estrogen is derived in part from that secreted with the bile and partly from direct excretion into the intestine [96] The recovery rate of endogenous and exogenous estrogen is the same for *men and women*[14] *and is not affected by the presence or absence of the* ovaries or uterus [170] The failure to recover significant amounts of injected estrogens is not due to storage in the organism [14]

Pearlman[109] points out that the catabolism of estrogens also results in the formation of products lacking in biologic activity He believes that this process of inactivation is to be distinguished from that of conjugation The nature of the substances produced by catabolic degradation of estradiol is not completely known The compounds produced by conjugation are normally excreted in the urine Themselves weakly estrogenic their full estrogenic potency is liberated by boiling the urine with hydrochloric acid

The discovery by Smith and Smith [25] that the estrogenic potency of certain urine specimens can be markedly increased by the addition of zinc dust prior to acid hydrolysis represents an important advance in the elucidation of the character of estrogen catabolites These workers *believe that this* procedure rehydrogenates certain non-estrogenic oxidation products back into chemical compounds with estrogenic activity While the reconversion of estrone to estradiol may account for part of this increased estrogenic activity they are of the opinion that a good portion of the increase is due to the presence of as yet unidentified oxidation products of estradiol Further experiments by Heard and Saffran [96] with human pregnancy urine and model aqueous solutions of estrogens appear to confirm the presence of an inert estrogen precursor in the complex conjugate mixture in human urine The nature of such precursors or oxidation products of estradiol is unknown but one of these may be lactone a compound obtained by Westerfeld[37] by treating estrone with hydrogen peroxide O W Smith [38–39]

gens from the circulation with a speed which varies with the conditions of the experiment and the species of animal employed. Data derived from observations of Szego and Roberts[181, 182, 183, 184] suggest a further hepatic role in estrogen metabolism. From a series of studies concerning the nature of circulating estrogens these workers believe that there is an equilibrium between physiologically inactive protein-bound estrogens and active estrogens in the form of a conjugate. About two thirds of the circulating estrogen is believed to be bound to protein. This serves as a readily available source of active estrogen as the latter is removed by the tissues. It is postulated that the liver functions in the formation of this protein-complex and that therefore the liver is essential for estrogen activity. At the same time the liver appears to prevent active estrogens from reaching the systemic circulation in large amounts.

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in the animals themselves may lead to discordant results. Moreover, identical methods of administration to different species lead to different assay units. Even the method of hormone administration (single or multiple dose, oil or aqueous vehicle) affects its estrogenic activity in the test animal.[207] Finally, since the individual estrogens vary in their estrogenic potency, the total estrogen content of a sample determined by bioassay does not necessarily correspond to that obtained by chemical assay. This applies particularly to studies of human pregnancy urine where there is a large excretion of estriol, the least potent of all three estrogens. In general, results obtained by bioassay methods are slightly lower than those secured by chemical assay.

Attention is called to the fact that rat or mouse units obtained by bioassay in one laboratory are usually not comparable to those obtained in others. It is advisable, therefore, to express results in terms of estrone. This is done by comparing the results obtained in the test material with *those obtained with known doses of crystalline estrone*. *The Health* Organization of the League of Nations has set up a set of international *standards for sex hormones, one of which is estrone*. *The international* unit for crystalline estrone is defined as the specific estrus-producing activity contained in 0.1 microgram. Therefore, 1 milligram of estrone equals 10,000 international units. The results of bioassays become more meaningful and susceptible to comparison when they are expressed in terms of the international reference standard for estrone.

Estimation of estrogens circulating in the blood of non-pregnant women is difficult and unsatisfactory because of the very low concentrations. Procedures are further complicated by the fact that approximately two-thirds is bound in a protein-complex.[151–154] Frank and his coworkers[64, 68] first detected the presence of an estrogenic substance in the peripheral blood. Subsequently, Frank and Goldberger[69] demonstrated an abrupt rise in blood estrogens between the tenth and fifteenth day of the menstrual cycle. They *related this observation to ovulation*. *Rakoff*[76] *has demonstrated* a progressive rise in the blood levels of estrogens during pregnancy. Blood levels are low in childhood and after the *menopause*. They may be elevated in hyperestrogenism due to granulosa cell or theca cell tumors of the ovary.

Estrogens in the urine have been more widely studied than in the blood. The pioneer observations of Frank and his colleagues[68, 70] and Loewe and Lange[408] indicated that the urinary content of estrogen varies during different times of the menstrual cycle, being highest at about the middle. Subsequent determinations made by various workers throughout a menstrual cycle[206, 210–218] indicate that there are two peaks of excretion, one in the intermenstrual period related to ovulation and the other premenstrually. The second peak is due to renewed follicle activity, this time as a corpus luteum. It is not known whether this second peak of urinary excretion is *due to an actual increase in the amount of estrogen formed or* to the sparing effect of progesterone which is secreted at this time. Smith and his collaborators[14] present evidence suggesting that progesterone prevents destruction of estrogen in the body and facilitates the conversion of estradiol to estrone to estriol which is more readily excreted. A marked variation in the location of the second peak has been recorded by different

found that lactone is much less estrogenic than estrone but apparently more effective in stimulating the adenohypophysis.

Estrogen Levels in the Blood and Urine.—It may be stated at the outset that estrogen determinations in the normal woman or man are hampered by the relatively minute quantities present. In an effort to detect these small amounts numerous methods have been devised. These have been comprehensively reviewed by Pincus[193] and consist essentially of chemical, physical and biologic procedures. For assay of body fluids such as blood and urine only the chemical and biologic methods are practicable at the present time. The physical methods include ultraviolet and infrared absorption spectrophotometry and polarographic assay. Both chemical and biologic methods of urinary assay require preliminary hydrolysis by boiling with acid. This is necessary in order to liberate the free estrogens from their conjugated forms (sulphate and glucuronide). It must be emphasized that this procedure results in considerable destruction and alteration in structure with a loss in the yield.

Several chemical methods have been developed which are based on an estrogen color reaction. This was first described by Kober[199] who found that phenolsulfonic acid reacted with estrone and urinary extracts to give a pink color. Sulphuric acid reacts in a similar manner. The numerous modifications relate to purification of the source of the estrogen and its final extraction. The principal difficulty of the chemical methods is due to the presence of non specific urinary chromogens which give a brown color and interfere with the reading of the pink color reaction of the estrogen. The recent efforts of Salter and his coworkers [00] appear to have been successful in overcoming this chromatic difficulty. They removed most of the interfering pigments by suitable solvent extraction after the Kober color reaction was obtained. As a rule, however, none of the chemical procedures are applicable to specimens from normal women or men. They are useful principally in the assay of late pregnancy urine. An important advance in the development of a chemical procedure for estrogen assay came with the recognition that sulfuric and phosphoric acids cause characteristic fluorescence when heated with estrogens. Accordingly, Jailer [01, 0] Finkelstein and his collaborators [03, 04] and Bates and Cohen [4] independently and simultaneously devised fluorometric methods for the determination of estrogens. These are extremely sensitive and are ideal for the detection and quantitation of the very small amounts of estrogen normally present in biologic fluids. Jailer[200] and Finkelstein [04] have adapted this micro method to urinary assays.

Numerous biologic assay methods are in use. Most are based on the original Allen Doisy [20, 06] vaginal smear technique. In essence, these procedures depend upon the ability of the estrogen containing extracts to cause a response (cornification) in the vaginal spread. Other methods employ different test animals and criteria of activity. The latter include increase in uterine weight and water (of the rat) and the disappearance of the vaginal closure membrane (of the guinea pig). All methods of bioassay have inherent difficulties which interfere with accurate estimations. For example, substances are present in urine extracts which may inhibit or enhance the activity of the contained estrogens. Furthermore, variations

of ovarian secretory failure are more marked if this occurs before rather than after puberty

Prepuberal estrogen deficiency is characterized by genitalia of childhood size with preservation of the infantile cervico-uterine ratio. As a result of poor or absent mammary stimulation the breasts remain undeveloped. Pubic and axillary hair growth is sparse while corporal and cranial hair development is normal. A generalized deposition of fat frequently occurs. Striking changes in skeletal development may occur. The pelvis fails to enlarge. The subject may become excessively tall due to failure of epiphyseal closure. In this event the extremities become disproportionately long in comparison with the torso so that the arm span exceeds the height. This type of skeletal abnormality is reminiscent of that which occurs in prepuberal androgen deficiency in males and is accordingly referred to as *ovarian eunuchoidism*. On the other hand the subject with prepuberal estrogen deficiency may fail to attain a normal height and may remain permanently undersized. This occurs in females with ovarian agenesis, a congenital abnormality associated with a somatic growth defect also presumably congenital in origin. A further osseous effect of estrogen deprivation is the ultimate development of osteoporosis.[55,78,79]

Postpuberal estrogen deficiency often produces no recognizable objective changes for a long time. Except for scant or absent menses and sterility such an individual may be indistinguishable from a woman with normally functioning ovaries. Eventually, however, the uterus becomes small and fibrous and the endometrium becomes atrophic. The vagina ultimately shows a reduction in volume and an atrophy of its mucosa. Regressive changes slowly occur in the breasts. The genital and mammary changes may require several years to develop. A slight regression in the amount of pubic hair may also occur. Vertebral osteoporosis is an occasional finding.[55-79] The slow rate of mammary decline and change in body hair observed in the postpuberal ovariectomized woman may be due in part to continued estrogen production by the adrenal cortex.[80]

The primary action of the estrogenic hormones in the animal organism is to promote growth of the accessory genitalia and breasts. This is accomplished by an acceleration of blood flow and increased rates of synthesis of new protein and organic elements. While the principal hormonal effects occur in the genital system and the breasts, important additional influences are observed on the tissues of other organs as well as on metabolic processes. Synthetic estrogens such as stilbestrol produce all or most of the effects of the natural estrogens.

Genital Effects.—Those organs which are derived from the embryonic Mullerian duct system are particularly responsive to estrogenic stimulation. These include the fallopian tubes, uterus and upper part of the vagina. The stimulating effect of estrogens on these structures is readily demonstrable by the colchicine technic. This substance has the property of arresting dividing cells in the metaphase, thereby causing an accumulation of many mitotic figures.[7] It does not stimulate mitosis itself but permits observation of any marked increase of mitosis which might occur as a result of growth stimulation. Its use has shown increased cell division in the target organs (uterus, tubes, vagina) upon which estrogens act.

workers ranging from early in the luteal phase to just before menstruation.

The total amount of estrogen excreted during a menstrual cycle has been reported to be 1.3 mgm.[17] and 1.67 mgm.[214] in terms of estrone equivalent. The maximum excretion on any one day was found to be 90[17] and 126[18] micrograms as estrone equivalent. In general, there is a substantial daily variation in the urinary excretion of estrogen. The average daily excretion in normal women ranges from a low of 5 to 15 micrograms to a high of 40 to 100 micrograms expressed as estrone, depending upon whether determinations are based on biologic or chemical assays. It is thus apparent that the clinical significance of results of single twenty-four hour urine assays must not be unduly emphasized. The urinary excretion of estrogens rises gradually during pregnancy so that near term excessive quantities are present. Estrogens are also excreted by males, but in amounts somewhat smaller than those found in normal nonpregnant women. Still smaller amounts are excreted by children of both sexes. They attain normal levels at the time of puberty. Of interest is the fact that newborn babies excrete large quantities of estrogen for a few days.[18] This is apparently derived from maternal sources. The urinary excretion of estrogen in women past the menopause usually remains at low normal levels.

Excessive quantities of urinary estrogenic hormone have been found by Frank[107, 19] in 4 patients with adrenal carcinoma. A similar finding was reported by Simpson and Joll[220] in a male with adrenal cortical carcinoma. However, not all cases of adrenal carcinoma are accompanied by an increased urinary excretion of estrogens.[221] Furthermore, Soffer[222] points out that large quantities of urinary estrogens have been noted in patients with endocrine disturbances whose adrenals are not the site of a carcinomatous growth. Large amounts of estrogenic substances are presumbably excreted in the urine of certain women with granulosa cell or theca cell tumors of the ovary. This is not surprising in view of the markedly estrogenizing effect of some of these tumors. An excessive excretion of urinary estrogens is occasionally noted in men suffering from testicular tumors.[223, 224, 225] This is particularly apt to occur when there is an associated increased excretion of chorionic gonadotropin in the urine, suggesting an origin of both hormones from embryonal tissue of chorionic type.

Biologic and Metabolic Effects of the Estrogens.—Woman is indebted to her estrogenic hormones for the growth and development of her accessory genital organs (uterine tubes, uterus, vagina, labia and Bartholin glands) and secondary sex characteristics. The latter include her feminine contour, high pitched voice, the development of breast tissue and the characteristic distribution of the pubic hair. The body and cranial hair are modified rather than initiated by estrogens.

The normal biologic effects of estrogen in the human female are most apparent when they are absent. Since estrogen secretion does not become effective until the age of puberty, it is only after the age of fourteen or fifteen years that evidences of estrogen deficiency usually become evident. The manifestations displayed by the estrogenically deficient woman depend to a large extent upon whether ovarian insufficiency supervened before or after the completion of puberty. In all instances estrogen deficiency results in sterility and sparse or absent uterine bleeding. The consequences

tic.[65-66] On cross section the endometrium appears vacuolated and is therefore known as a "swiss-cheese endometrium." A similar glandular cystic hyperplasia is encountered in women whose ovaries contain one or more persistent vesicular follicles. Instead of discharging an ovum and becoming transformed into a corpus luteum, these follicles persist in an actively functioning state and continue to secrete increased amounts of estrogen.

Estrogens also contribute to the growth of the myometrium during adolescence and pregnancy. Their effect on muscle contractility in the human is still a moot point. It has been shown by Reynolds[30] that a rhythmic uterine motility exists in certain intact animals. In general, estrogen stimulates contractility while progesterone inhibits it. Uterine motility disappears after castration and can be restored by estrogen administration. The estrogenic effect on uterine motility in these animals can also be offset by progesterone.

The natural or artificial menopause is followed after a variable length of time by a general atrophy of the uterus and vagina whereby these organs become firm and fibrous. It is to be noted, however, that striking degrees of endometrial hyperplasia may be observed years after the menopause.[33] Vaginal smears may show evidence of estrogenic activity for several years after the menses have disappeared. It cannot be stated with certainty whether this is due to residual ovarian secretory activity or to estrogens of adrenal origin.

Effect on the Uterine Tubes. — The epithelium and muscular coat of the fallopian tubes are also stimulated by estrogen. Cyclic changes in motility appear to be conditioned by the hormones of the ovary,[31] although the mechanisms of action have not yet been elucidated.

Effect on the Ovaries. — The effect of estrogens on the ovaries themselves depends largely upon the amount to which the organism is subjected. As previously stated, small quantities are essential under normal conditions for follicle maturation. Again, under physiologic conditions, somewhat larger amounts exert an indirect effect on follicle development through their effect on the character and extent of adenophypophyseal gonadotropin secretion. In other words, the increasing levels of estrogen which become available during the pre-ovulatory phase result in an enhanced gonadotropin secretion, chiefly in the form of LH. This effect has been noted in the experimental animal where estrogen treatment has been shown to result in an increased LH content in the assayed adenophypophysis.[243] When large amounts of estrogen are administered, the effect on the ovary is a decidedly inhibitory one. Follicle development is markedly suppressed as a consequence of pituitary gonadotropin inhibition by the large quantities of estrogen. This has been demonstrated in the laboratory animal by Moore and Price[244] and by Nelson.[39] As far as the ovaries are concerned, the effect of intensive estrogen therapy is equivalent to that of hypophysectomy. However, the ovaries may recover full function if the exposure to estrogens is not too prolonged or severe.[45]

The effects of estrogen on the human ovarian cycle have been investigated experimentally by Brown and his coworkers.[405] Alterations of the cycle vary with the mode of estrogen administration. A single large dose (10 to

Effect on the Vagina.—The effect on the vagina is to cause growth of the epithelial layer with thickening, stratification and cornification. This reaction in the spayed mouse or rat is the basis of most estrogenic bioassays.[6, 68] Microscopic examination of vaginal smears containing exfoliated epithelial cells readily indicates the advent of an estrogenic influence. Papanicolaou[78] extended these observations to women and was able to correlate changes in the smears with various phases of the sex cycle. With Shorr[79] he subsequently demonstrated the value of the vaginal smear in the human as a guide to estrogenic therapy. Associated with epithelial proliferation there is a deposition of glycogen within the cells. Its decomposition to lactic acid causes the vaginal secretion to assume an acid reaction of pH approximately 4 to 5. In addition to the epithelial changes, the vagina as a whole enlarges in the adolescent girl as a result of the appearance at this time of ovarian estrogenic secretion.

Prepuberal stimulation of vaginal growth by the local application of estrogen has been employed therapeutically. The gonococcus grows easily in the infantile vagina causing a vaginitis. On the other hand, its growth is inhibited by mature vaginal epithelium with its glycogen content and acid secretion. For this reason the temporary induction of an adult type of mucosa is effective in eradicating gonorrheal vaginitis in children.[37] In the light of current results with antibiotics, this form of therapy is no longer indicated.

Effect on the Uterus.—The effect on the uterus is also that of growth and differentiation. At puberty, under the influence of the newly appeared ovarian estrogen, the uterus enlarges and prepares to engage in its important role in the reproductive cycle. The influence of estrogen is much more apparent in the endometrium than in the myometrium. This has been described in detail in the preceding chapter (p. 541). In summary, it may be said that the epithelial cells which line the surface and those which line the glands undergo proliferation. The cellular constituents and spiral arterioles of the endometrial stroma also participate in the growth reaction so that the total effect of estrogenic stimulation is to produce a thickened vascularized layer abundantly supplied with glands. There is also an increase in intercellular fluid. These changes occur physiologically during the menstrual cycle and can be reduplicated artificially in the ovariectomized woman by the administration of estrogens. The sharp reduction in circulating estrogen which occurs premenstrually is responsible for the endometrial regression which leads to menstruation with sloughing of most of the endometrium. This effect can also be reproduced in the castrated woman or animal. In such cases the continuous administration of estrogen causes a proliferation as described above. Four or five days after cessation of treatment, endometrial involution results in necrobiosis and bleeding, the well known "withdrawal bleeding."

The long-continued administration of estrogens results in abnormal changes in endometrial structure. In rats, a metaplasia of the uterine epithelium is produced which undergoes stratification and cornification similar to that of the estrous vagina.[64] Prolonged treatment in rabbits, guinea pigs and monkeys causes a marked endometrial hyperplasia which involves the glands to such an extent that they become dilated and cys-

pregnancy because of the inhibitory effect of the large amounts of estrogens prevailing at that time. The decrease in systemic estrogens consequent on parturition releases the adenohypophysis and permits prolactin to initiate lactation. The continued administration of estrogens (natural or synthetic) after parturition results in the prompt suppression of milk production. This has been amply demonstrated in the lactating cow [49] and in the human [0, 34]. Clinical application of this action has been made in parturient women who do not breast feed their babies.

General Metabolic Effects.—These are not as well-defined as the known effects of the androgenic hormones in the male. Neither have they been as extensively studied. Estrogens exert their principal extragenital effects on the osseous system and on electrolyte metabolism. As a corollary of the latter, water balance is influenced.

The estrogenic hormone accounts for the characteristic female skeleton with its broad pelvis. It also has a marked effect on linear bone growth comparable to that of testosterone. Centers of ossification mature more readily and epiphyses close earlier under its influence. The reverse of these effects is known from observations in women who were deprived of their normal estrogen supply prior to the completion of puberty. These subjects show a retardation of bone age as evidenced by failure of epiphyseal union due to delayed ossification. At the same time in certain cases the bones of their extremities may grow excessively long resulting in tall individuals with limbs which are disproportionately long in comparison with the torso. This comes about as a result of the open epiphyses which permit linear growth to continue beyond the usual chronologic age of puberty. It is apparent in these cases that the increased bone length is due to extragonadal growth factors which are enabled to exert their influence over an abnormally long period of time. Conversely, Hamblen [33] points out that the growth of a child subjected to excessive amounts of estrogen from a granulosa theca cell tumor is checked at an earlier level than the average.

One effect of estrogen-deficiency on bone metabolism is well exemplified by the vertebral osteoporosis which appears in some women with ovarian insufficiency. [79] Albright and Reifenstein [5] hold that this is due to defective osteoblastic activity and not to a disturbance in calcium metabolism.

The mechanism by which estrogens act on the osseous system is imperfectly understood. Available experimental data are meagre and conflicting. For example, a marked increase in serum calcium has been noted in association with spontaneous ovarian activity in pigeons and doves [26] and after the administration of estrogens to rats and mice. [57, 6] On the other hand injection of estrogens into several mammalian species failed to produce a significant change in blood calcium levels. [38] Finally, a decreased blood calcium was observed in lactating cows after the administration of large doses of estrogen. [49] In the human, injections of large amounts of estrogen result in a retention of calcium. A decreased urinary excretion of calcium and phosphorus has been noted in women with postmenopausal osteoporosis after the administration of estrogen. [3] A marked and dangerous hypercalcemia has been reported following the use of large doses of estrogens in the palliative treatment of mammary cancer in women. [9] Androgens resemble estrogens in this ability to retain calcium in the human. In addition

20 mg. of stilbestrol orally) given *early* in the cycle delays ovulation for about ten days and increases the length of the cycle to the same extent. The daily oral administration of 1 to 3 milligrams of stilbestrol continuously for thirty days completely inhibits ovulation. When estrogens are given *late* in the cycle no effect on the luteal phase is observed. Even the administration of large doses (10 mg. of stilbestrol daily) fails to maintain functional corpora lutea as indicated by the onset of menstruation at the expected time.

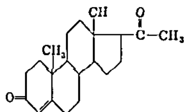
Effect on the Breast.—Strictly speaking, the breasts are not truly genital organs, but they exhibit a characteristic sensitivity to estrogens. The estrogenic hormone is responsible for the physiologic hypertrophy of the breasts which heralds the advent of puberty. The glandular structure of the breasts also undergoes cyclic fluctuations which are synchronous with the cyclic variations in estrogen secretion by the ovaries. The effects of estrogens on mammary growth has been studied extensively in the experimental animal of both sexes. Despite many species differences, it is uniformly true that the estrogenic hormone stimulates duct growth. On the other hand its ability to influence the formation of lobule-alveolar tissue is quite variable, being absent in some animals and potent in others.[46] In many animals as well as in women estrogens produce some growth of the lobule-alveolar system in addition to duct formation. However, complete growth of the mammae requires the presence of the second ovarian hormone, progesterone. It is this secretion which complements the duct-forming effect of estrogens by causing the development of the lobules and alveoli.

There is a considerable divergence of opinion as to the mechanism by which ovarian hormones stimulate mammary growth. Most of the controversy centers about the role of the pituitary in breast development. Although Folley and Malpress[46] point out that no final statement can be made as yet concerning this issue, a large body of evidence has been accumulated to support the mammogenic theory of Turner and his collaborators.[3, 4] These workers claim that estrogen and progesterone in certain species of animals stimulate the adenohypophysis to secrete specific "mammogens" or hormones which in turn influence the breasts. Estrogen evokes mammogen I, the "duct growth factor," while progesterone assists in the elaboration of mammogen II, the "lobule-alveolar growth factor."

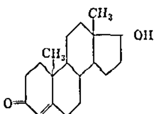
Apart from the effect of estrogens on mammary structure they also exert an indirect effect on the secretory function of the breast. The ability of the breasts to secrete milk requires, in the first place, an adequately formed parenchyma. Following the development of a suitable anatomic substrate, normal milk production is dependent on a number of complex metabolic and hormonal processes. These have been extensively reviewed by Folley and Malpress[47] and are not germane to the present discussion. It is relevant at this point, however, to point out the effect of estrogen on lactation. One of the hormonal factors involved in the control of lactation is the adenohypophyseal lactogenic principle prolactin. It is identical with luteotropin, the gonadotropin which controls corpus luteum function. Large quantities of estrogens have the same inhibitory effect on this pituitary principle[248, 49] that they have on the other gonadotropic factors. It is believed by Nelson[48] that lactation does not occur during the last stages of

The Hormone of the Corpus Luteum.—Although it was known for a long time that pregnancy is associated with the presence of large persistent corpora lutea, it was not until 1903 that Fraenkel[67] showed that the corpus luteum is essential for the continuation of early pregnancy. Shortly afterward Marshall and Jolly[62] recognized that there are two different ovarian hormones, one estrogenic and the other progestational. An actual progestational effect on the endometrium during pregnancy was demonstrated histologically in 1910 by Bouin and Ancel.[68]

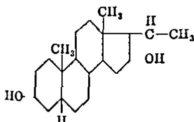
It remained for Corner[69] and Corner and Allen[70] to prove that the corpus luteum prepares the uterus for implantation of a fertilized egg. These workers accomplished this by injecting extracts of corpora lutea from pregnant sows' ovaries into ovariectomized adult rabbits. A characteristic progestational endometrial response was obtained which has since become recognized as the physiologic end point in the action of the corpus luteum hormone. Once proof of the existence of a luteal hormone was established it was not long before the hormone itself, progesterone, was isolated and identified. This was accomplished simultaneously and inde-



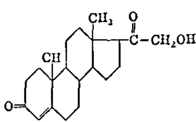
Progesterone



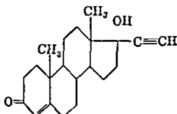
Testosterone



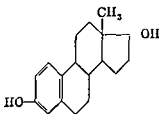
Pregnanediol



Desoxycorticosterone
(21 hydroxyprogesterone)



Anhydrohydroxyprogesterone
(pregneninolone, ethinyltestosterone)



α-estradiol

FIG. 54—Structural formulas of progesterone and some related compounds showing their relationship to estrogens and the steroidal hormones of the testis and adrenal cortex

these steroid hormones favor the retention of nitrogen and phosphorus and are accordingly useful in the prevention and therapy of senile and postmenopausal osteoporosis, in the acceleration of fracture healing in older patients, and in increasing the rate of somatic growth in certain hypogonadal individuals.

Apart from changes in the serum calcium, observations in the experimental animal show a direct effect of estrogens on bone resulting in the stimulation of osteoblastic activity. Precocious closure of the epiphyses of dogs[61] and mice[6] are noted after the administration of estrogens. In the latter animals the greater part of the marrow cavities is replaced by a proliferation of new bone. The reader is referred to the excellent reviews by *Gardner and Pfeiffer*[60] and by Albright and Reifenstein[-] *for a detailed* account of the influence of gonadal steroids on the skeleton.

The excretion of electrolytes and nitrogen is affected by the estrogenic hormone. Knowlton and her coworkers[1] demonstrated the anabolic effects of estrogen. The administration of estrogen to humans with ovarian insufficiency resulted in the retention of sodium, nitrogen and phosphate. In women with postmenopausal osteoporosis, natural and synthetic estrogens *produce a retention of calcium, phosphorus and nitrogen*.[-] *Thorn and* his coworkers[63] demonstrated a correlation between the urinary excretion of estrogen throughout a menstrual cycle and the blood electrolytes and water balance. A retention of electrolytes and water prior to menstruation accounts for the well known premenstrual weight gain and edema that occur in some women. The anabolic effects of estrogens are similar to those produced by testosterone, although they accomplish their osseous effects in different ways. Estrogens primarily stimulate osteoblastic activity, while the principal influence of androgens is on the integrity of the bone matrix by *favoring nitrogen retention*.[-] *The general effects of estrogens and* androgens on electrolyte metabolism are similar to but much less marked than those of certain adrenal cortical hormones.

Additional miscellaneous effects of a general metabolic nature following the administration of estrogens include those on the skin, blood and vascular system. Cutaneous edema follows the local application of stilbestrol ointment in the hairless mouse. On the other hand, a loss of skin turgor is often noted in ovariectomized women. The injection of estrogen results in decreased sebaceous gland activity,[[illegible]] an effect opposite to that evoked by *testosterone*.[84]

The administration of estrogens to female dogs induces anemia,[[illegible]] apparently as a result of bone marrow destruction. *Comparable effects in the* human are lacking. Interestingly enough, androgens have a stimulating effect on blood production in the human. The hypogonadal male responds with an improvement in his erythrocyte count.[86] Androgen therapy in inoperable female mammary carcinoma occasionally produces an actual polycythemia.[87]

In addition to the hyperemic response induced in genital organs by estrogens, a similar effect occurs peripherally. Reynolds[55] has measured vasodilatation induced in rabbits and humans by estrogens.

A detailed analysis of the biologic and metabolic effects of estrogens may be found in the extensive reviews by Allen, Hisaw and Gardner,[2, 9] Pincus,[50] and Paschkis and *Rakoff*.[407]

Progesterone itself does not appear in the urine. On the other hand, several metabolic reduction products have been isolated from the urine. Principal among these is pregnanediol, which is found in the urine of normal women during active periods of progesterone secretion. These are the luteal phase of the menstrual cycle and pregnancy. A correlation exists between corpus luteum and placental activity on the one hand and the urinary excretion of pregnanediol on the other. This is close enough to warrant the use of pregnanediol excretion as an index of progesterone secretion and the rate of its metabolism. Nevertheless, as Marrian[9] points out, the relationship is not constant and cannot be relied upon with certainty.

Pregnanediol is excreted in a conjugated form as the sodium salt of pregnanediol glucuronide.[292] The glucuronic acid linkage occurs at the C-3 position. Pregnanediol makes its appearance in the urine when the corpus luteum first begins to secrete progesterone, i.e., at the time of ovulation. Its excretion reaches a peak during the premenstrual phase of the cycle.[94] The amounts excreted vary according to the particular method of assay employed. Expressed as free pregnanediol, Venning[315] finds 4 to 16 mg. in the forty-eight hour urine specimens obtained during the luteal phase. In a study of 15 normal menstrual cycles employing the Atwood-Jones procedure,[98] Jones[99] found average low and high values of 6.2 mg. and 10.7 mg. of free pregnanediol per forty-eight hours during the luteal phase. The urinary content of pregnanediol decreases a few days before the onset of menstrual bleeding and is absent or present in minute amounts during the follicular phase of the cycle. A large output of pregnanediol occurs as pregnancy progresses, reaching levels which average between 50 and 100 mg. per twenty-four hours at term.[311] Excessive amounts of pregnanediol may be excreted in the urine of patients with adrenal tumor and hyperplasia.[311,312,314] Mason and Kepler[313] found pregnanediol 3(α), 20(α) in all but 1 of 10 females with adrenocortical hyperfunction. In 2 patients the 3(β), 20(α) isomer was also tentatively identified by melting point studies. The quantities of pregnanediol excreted suggest that tumors and hyperplasia of the adrenal cortex may result in the relatively large production of progesterone or other precursors of pregnanediol, such as desoxycorticosterone, or both.

Pregnanediol is absent from the urine of healthy men. Its presence has been reported, however, in the urine of a man with a chorionepithelioma of the testis. Twombly[314] found this patient to excrete from 10.5 to 16.5 mg. per forty-eight hours of a substance identified by its melting point and mixed melting points as probably free pregnanediol.

Metabolism of Progesterone.—Little is known concerning the anabolism of this hormone. Its steroid nucleus suggests an origin from cholesterol. This possibility gains support from the studies of Bloch[316] who administered deuterium labelled cholesterol to a pregnant woman and recovered isotope-containing pregnanediol in the urine. Since pregnanediol is a product of progesterone catabolism, it was suggested that the direct conversion of cholesterol to progesterone may occur under normal physiologic conditions. An entirely different approach also suggests cholesterol as a metabolic

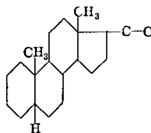
pendently by Butenandt and his colleagues [71] Allen and Wintersteiner Slotta and his collaborators[2,3] and Hartmann and Wettstein[2,4] in 1934 Progesterone the pure hormone of the corpus luteum is to be distinguished from progestin The latter is a generic term applied to a variety of chemical compounds having a biologic action comparable to that of progesterone [15, 3]

Progesterone is formed principally but not entirely by the corpus luteum of the ovary Since this structure is derived from the granulosa and theca cells of the follicle [5, 6] these cells are believed to elaborate the hormone Parenthetically it is to be remembered that estrogen (estradiol) continues to be secreted by the follicle cells even after they become luteinized

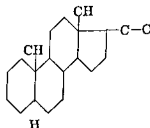
The adrenal is another source of progesterone The hormone was isolated from the adrenals of oxen in 1938 [90, 91] Pure progesterone has not as yet been obtained from the placenta but there is a considerable amount of circumstantial evidence indicating that this structure elaborates an active progestational hormone [15, 9] During the later stages of pregnancy the placenta appears to be the major source of progesterone

The chemical structure of progesterone is related to that of the natural estrogens androgens and adrenocortical steroids The basic structure of the steroid nucleus was described in the section dealing with estrogens The chemical formula for progesterone is illustrated in figure 54 which also indicates its relationship to its principal derivative and to the other steroidal hormones It is apparent that its chemical composition is more closely related to testosterone and the adrenal cortical steroids than it is to estrogen The single double bond in ring A the two angular methyl groups and the side-chain at the C 17 position account for these chemical similarities

One of the principal structural changes which occurs during the metabolism of progesterone is the saturation (hydrogenation) of the *pregnene* nucleus resulting in the elimination of the double bond in ring A This produces a saturated nucleus which belongs to the *pregnane* series In this manner an additional pair of stereoisomers is permitted depending on the spatial position of the hydrogen atom attached at the C 5 position The conventional pregnane compounds are characterized by the *cis* position of the C 5 hydrogen above the plane of the rings It is designated by a solid line valency bond The stereoisomeric compounds with reference to the C 5 hydrogen atom are the *allo*-compounds where the hydrogen atom occupies a position below the plane of rings In this case the valency bond is indicated by a dotted line as illustrated



Pregnan



Allo p g
Se ie

mester of pregnancy than in the non pregnant state Guterman[104] reports that whereas the non pregnant, pre-ovulative woman excretes 10 to 15 per cent of 100 mg of injected progesterone as pregnanediol the normally pregnant woman excretes between 25 and 35 per cent In the experience of this worker an excretion of only 10 to 15 per cent during the early months of gravidity is a bad prognostic sign in cases of habitual or threatened abortion Under these circumstances abortion may be expected These observations suggest that in disturbances of pregnancy the conversion of progesterone to pregnanediol may serve as an index of the integrity of the gestational process

Pearlman[92] has reviewed the evidence which suggests the liver is the major site for the biologic inactivation of progesterone However the liver does not inactivate progesterone *in vitro*[306 307]

Pregnanediol is the chief metabolic product of progesterone Two other compounds are also known to undergo metabolic transformation into pregnanediol These are desoxycorticosterone and Δ pregnenol 3(β)-one 20 Despite the administration of massive doses of all three compounds no substance other than pregnanediol 3(α) 20(α) has been recovered in metabolism studies This is remarkable in view of the fact that several pregnane derivatives have been isolated from the urine during pregnancy a period of high progesterone secretion Curiously enough, the orally active progesterone compound pregneninolone (anhydrohydroxyprogesterone) is not transformed into pregnanediol[309]

The two known metabolic end products of progesterone metabolism pregnanediol and pregnanolone are excreted in the urine as conjugates of glucuronic acid conjugation presumably occurring in the liver[292] The conjugated compounds are referred to by Venning[310] as the pregnanediol complex Separation of the larger pregnanediol fraction is accomplished by hydrolysis of the glucuronidates and subsequent colorimetric or gravimetric analysis for free pregnanediol Both free and conjugated pregnanediol are biologically inactive

The biologic activity of progesterone is not highly specific in that its progestational activity is retained even after considerable chemical alteration Essential for its activity is the 3 keto-Δ^4 structure The potency of progesterone has been established in accordance with an international standard The International Unit is defined as the specific progestational activity of 1 0 mg of the international standard preparation of progesterone

Progesterone is not active after oral administration This is due to intestinal as well as to hepatic inactivation It is therefore usually administered intramuscularly in an oil solution However a synthetic preparation pregneninolone (anhydrohydroxyprogesterone 17-ethinyltestosterone) is effective on oral as well as parenteral administration It has about one fourth the progestational activity of progesterone

Biologic Effects of Progesterone —Since the corpus luteum is essentially a mechanism for pregnancy its secretion exerts its influence principally on the uterus Collateral effects on the breasts and ovaries play a supplementary role

precursor of progesterone[119] Experiments based on the cholesterol content of rats ovaries point to a correlation with the secretion of progesterone

The urinary excretion of pregnanediol following the administration of desoxycorticosterone to normal men[301] suggested that this adrenocortical hormone is a possible precursor of progesterone This metabolic conversion has been proven recently in the intact monkey by the demonstration of increased blood levels of progesterone following the administration of desoxycorticosterone[307] The well known progestational activity of the latter compound may be explained on this basis

Progesterone has also been synthesized in the laboratory from stigmasterol (a sterol obtained from soy bean oil) and from pregnanediol

Like the parent estrogenic and androgenic hormones, progesterone is secreted in fairly large quantities almost or quite continuously during corpus luteal or placental activity It is not stored in the organism but is utilized metabolized and excreted almost immediately so that only minute quantities are present in the circulating blood Excretion in the urine occurs only in the form of metabolites These have been studied principally in the pregnant human and animal where the secreted amounts are large enough to be subjected to qualitative analysis Additional data have also been obtained from excretion studies following the administration of progesterone and related compounds

One of the chief products of progesterone metabolism in the human is pregnanediol so-named because it was first isolated from human pregnancy urine[300] Several related pregnane compounds are also found in the urine of pregnant women Only one of them pregnanolone is definitely known to be a metabolic product of progesterone although all of them are assumed to be similarly derived[95] The stereoisomers of pregnanediol and pregnanolone isolated from human pregnancy urine are the following

pregnanediol 3(α) 20(α)	pregnanol 3(α) one 20
allopregnanediol 3(α) 20(α)	allopregnanol 3(α) one 20
allopregnanediol 3(β) 20(α)	allopregnanol 3(β) one 20

An additional steroid suggested as a progesterone metabolite is allopregnanediol 3(β) 20(β) which has been isolated from normal ox bile[307] This finding points to the biliary tract as an accessory pathway for metabolite excretion

The administration of progesterone to men also results in the excretion of pregnanediol[303,304,305] and pregnanolone[305] However the proportion of the administered hormone excreted as pregnanediol in both sexes varies over wide limits but is usually rather low about 10 per cent[295] Marrian[295] points out that while the extent of conversion varies in different individuals it is remarkably constant in the same subject when the same route of administration is used The uterus and the ovaries are not essential for the conversion of progesterone to pregnanediol

The percentage urinary excretion of pregnanediol following the parenteral administration of progesterone appears to be greater during the first tri-

ably also present in humans.[370] This observation is the basis for the clinical use of progesterone in primary dysmenorrhea which is characterized by severe uterine contractions. A similar reason led to its use in threatened abortion. However in neither of these conditions has its therapeutic efficacy been definitely established.

Effects on the Vagina.—The action of progesterone on the vagina is neither important for gestation nor is it clearly understood. In many animals it produces mucification of the vaginal epithelium during pregnancy and pseudopregnancy. Its mucifying action is not demonstrable unless the vaginal mucosa has become stratified as a result of antecedent estrogenic stimulation. In the human Shorr and his collaborators[371, 372] have evaluated the effects of progesterone by studies of vaginal biopsies and smears of desquamated vaginal epithelial cells. These workers demonstrated stratification and cornification as a result of estrogen stimulation during the first half of the menstrual cycle. The same effect was noted after the administration of estrogens to the castrated or postmenopausal woman. During the second half of the cycle (luteal phase) cornification regresses but the entire width of the vaginal epithelium becomes markedly increased as a result of cellular proliferation. The effects of progesterone stimulation also become manifest in the vaginal smears. These show a decreased number of cornified cells and a marked tendency to cellular clumping. The non-cornified cells show a characteristic folding and curling of their edges. The same changes can be reproduced in women after the menopause by adding progesterone while estrogen administration is continued.

Action on the Breasts.—The breasts react in a distinctive manner to progesterone. Normal mammary growth is characterized by the development of ducts, lobules and acini. Duct formation (and in women some lobule and acinar growth) occurs as a result of the initial action of estrogenic hormone. Without preliminary estrogenic stimulation progesterone by itself lacks an effect on the breasts.[323] A single exception to this rule exists in male mice where progesterone alone causes an extensive duct system.[24] In woman as well as in most animals complete mammary development requires the presence of progesterone. This hormone reacts on the estrogen prepared mammae to cause the full development of the lobule alveolar system. The mechanism of this action is not clearly understood and was discussed in the section dealing with the effect of estrogens on mammary growth. There is substantial evidence suggesting that estrogen and progesterone stimulate the adenohypophysis to secrete specific mammogenic hormones.[3, 4] According to this theory estrogen causes the secretion of mammogen I, the duct growth factor, while progesterone leads to the elaboration of mammogen II, the lobule alveolar growth factor.

It is not known whether progesterone has an influence on the ability of the breasts to secrete milk. The results of animal studies dealing with the effect of progesterone on the prolactin content of the adenohypophysis are inconclusive.[247]

Effects on the Ovaries.—Progesterone has a clear-cut inhibiting effect on the ovaries themselves. This has been adequately demonstrated in animal experiments involving the removal of corpora lutea.[427, 328] As a result of progesterone in physiologic amounts ovarian follicles fail to mature and

Action on the Endometrium.—The characteristic effects of progesterone on the endometrium begin after the latter has proliferated as a result of stimulation by the estrogenic hormone. In fact, under physiologic conditions the cooperation of estrogen is an absolute requirement for the action of progesterone. Figuratively speaking, estrogens pave the way by inducing cellular hypertrophy and hyperplasia, especially of the endometrial glands. The latter are then stimulated to secretion by progesterone. These, in essence, are the successive proliferative and secretory phases which develop in the endometrium during the course of a menstrual cycle.

The development of the secretory phase of the endometrium under the influence of progesterone is essential for implantation of the fertilized ovum. During the luteal phase of the cycle, progesterone-induced endometrial changes consist of an increasingly marked secretory activity of the glands. The glandular epithelium develops deposits of glycogen which participate in the process of secretion. The glands themselves become markedly enlarged, widened and tortuous, assuming a corkscrew shape. The spiral arterioles become thicker and more coiled. Enlargement of the stromal cells occurs and the width of the endometrium is further increased by the appearance of edema.

In the absence of fertilization and nidation of the ovum, regression of the corpus luteum occurs with a resulting decrease in progesterone secretion. The withdrawal of this hormone (as well as the reduction in estrogens) is responsible for menstrual bleeding, during which the greater part of the prepared endometrium is sloughed.

In the event of fertilization of the recently discharged ovum, the corpus luteum and its secretory function is maintained for about three months. This is the length of time required for the full development of the placenta which assumes an important function in the elaboration of hormones necessary for gestation. The fertilized ovum is benefited by progesterone in two ways. Before implantation the normal development of the blastocyst is dependent upon adequate amounts of progesterone. This has been demonstrated in the laboratory animal where ovariectomy or extirpation of the corpus luteum alone prevents normal development of free uterine ova and their subsequent implantation.[316,317] After implantation the fertilized ovum is nourished by the progesterone-prepared secretory endometrium. The nature of this nutritional mechanism is not known, but the experiments of Pincus[318] suggest that the secretion of glutathione may be an important factor both before and after implantation.

Following nidation progesterone has a further effect on the endometrium in favoring the formation of the maternal part of the placenta. The progestational effects of progesterone on the endometrium have been amply substantiated by experiments involving the removal of corpora lutea and the injection of extracts containing progesterone. These have been reviewed at length by Allen and his collaborators,[59] Corner,[3] and Pincus.[260]

Action on the Myometrium.—The myometrium is also affected by progesterone. Under its influence spontaneous contractions of the uterine muscle diminish and the uterus is rendered quiescent. Corner[319] suggests that the inhibition of movement probably facilitates attachment of the embryo. The quieting effect of progesterone on the myometrium is prob

data For example fat soluble sow ovarian tissue contains androgenically active material[340] Furthermore mouse ovaries grafted into the ears of castrated male mice were shown to be capable of preventing involution of the accessory generative organs[341] It is interesting to note that transplantation of the ovaries into the abdomens of castrated male mice failed to maintain the accessories indicating that temperature is the important factor

PHYSIOLOGY OF MENSTRUATION

In the light of current concepts menstruation serves no known function Rather does it represent the frustrated expression of a uterus which had been prepared in vain for pregnancy This is true only if one adheres to the interpretation of the menstrual cycle held by most clinicians For example Hamblen[33] and others[342] regard periodic uterine bleeding as truly menstrual only when it is preceded by ovulation and the formation of a corpus luteum and a progestational endometrium Bleeding from the uterus at regular intervals without these antecedent phenomena is termed anovulatory bleeding However Novak[69] feels that this is an unsound distinction and that periodic physiologic bleeding from the uterine mucosa is true menstruation regardless of whether or not it was preceded by ovulation and corpus luteum activity

Cyclic anovulatory bleeding occurs frequently in certain monkeys especially during the non breeding summer months[65] It also occurs in women but is rare when their periods are regular[343] Bartelmez[6] has collected 17 acceptable cases from the literature in which corpora lutea were proven to be absent from the ovaries of women with regularly recurring periods Nevertheless it is to be emphasized that the characteristics of ovulatory and cyclic anovulatory uterine bleeding are usually indistinguishable The basic physiologic investigations of Corner[344] Bartelmez[56] and Markee[50–53] indicate furthermore that a progestational endometrium is not an essential prerequisite to regular uterine bleeding and that the underlying endometrial vascular changes leading to both types of bleeding are identical

Various phases of the histologic and physiologic aspects of the menstrual cycle have been described in previous sections It is proposed at this juncture to confine the discussion to a consideration of the factors involved in the process of menstruation itself The events which occur in the uterus are under the direct influence of cyclic fluctuations in ovarian hormonal secretion These in turn are dominated by the adenohypophysis It will be recalled that after ovulation a predominance of luteinizing hormone results in luteinization of the follicle and the formation of the corpus luteum The third adenohypophyseal gonadotropin luteotropin then becomes effective in establishing the secretion of progesterone The continued secretion of estrogen and progesterone during the second half of the menstrual cycle results in changes in the endometrium which characterize the luteal (premenstrual or progestational) phase

The corpus luteum attains its peak of activity about one week after its formation Its effective secretory activity continues until a few days be

ovulate. Estrous cycles in animals are suppressed. The continued administration of large quantities of progesterone results in atrophy of the ovaries. These effects are mediated through the adenohypophysis by inhibition of its LH secretion.[45] The lack of follicle development and amenorrhea of early pregnancy are explained on this basis.

General Metabolic Effects.—These have not been studied as extensively as they have been in the case of estrogens and androgens. A retention of sodium has been reported to follow the administration of progesterone and pregnanediol in the normal male dog.[329] In an adrenalectomized dog, chloride and water were retained in addition to sodium after a single injection of 20 mg. of progesterone.[330] The intact and hypophysectomized rat, however, show an increased excretion of water after treatment with progesterone. It is apparent that the influence of progesterone on the excretion of water may vary according to whether the adrenals are intact.

Progesterone may cooperate with estrogens in producing salt and water retention in the normal woman. The premenstrual weight gain[331] and edema experienced by many women may be in part due to the increased amounts of progesterone which prevail at this time. In view of the close chemical resemblance between progesterone and adrenocortical hormones, it is not surprising that the former is capable of maintaining life in male and female adrenalectomized animals of various species.[332–334]

Androgen Secretion by the Ovary.—It is very doubtful whether the human ovary normally produces androgens. On the other hand, it is well known that certain tumors of the ovary may elaborate large amounts of androgenic material enough to induce masculinization of the subject. This is true even when tumors originating from ectopic adrenal tissue are carefully excluded from consideration. Masculinizing ovarian tumors are quite rare and include the arrhenoblastoma and the sympathicotropic cell (Leydig cell or "hilus cell") tumor.[335, 336, 337] Since the former tumor is presumably derived from vestigial rests of male-directed embryonal germinal epithelium, its androgenizing effects do not relate to the secretory potential of the normal ovary. The situation with regard to the "hilus cell" tumors is not so readily disposed of. The hilus or sympathicotropic cells described by Berger[335] in the hilum of the normal ovary and the mesovarium are regarded as morphologically and histochemically indistinguishable from the Leydig cells of the testis. They are considered by some to be the source of male sex hormone which can be extracted from the ovary of certain probable experimental animals.

Data on the urinary excretion of androgens and 17-ketosteroids by ovariectomized women have not been consistent or revealing. Callow and his coworkers[338] found a reduction to one-half the normal values for the former and no change in the secretion of the latter. On the other hand, marked increases in the excretion of 17-ketosteroids have been reported from another laboratory.[339] Since a reciprocal relationship exists between the gonads and the adrenal cortex, no inferences can be drawn concerning ovarian androgen production in the presence of intact adrenals.

Although there is no conclusive proof that the human ovaries normally secrete androgen, observations in the experimental animal yield affirmative

data For example fat-soluble sow ovarian tissue contains androgenically active material [240] Furthermore mouse ovaries grafted into the ears of castrated male mice were shown to be capable of preventing involution of the accessory generative organs [241] It is interesting to note that transplantation of the ovaries into the abdomens of castrated male mice failed to maintain the accessories indicating that temperature is the important factor

PHYSIOLOGY OF MENSTRUATION

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The corpus luteum attains its peak of activity about one week after its formation Its effective secretory activity continues until a few days be

fore the next expected menses. During this time specific progestational changes occur in the endometrium which prepare it to receive and nourish a fertilized ovum. The lining of the uterus becomes markedly thickened principally as a result of hypertrophy and dilatation of the endometrial glands. These become larger, wider and tortuous, assuming a corkscrew shape. Their lining epithelial cells show evidence of increased secretory activity. Subnuclear vacuoles appear and are due to deposits of glycogen and mucin in the basal portions of the cells. The stroma increases in width partly through the appearance of edema and partly by hypertrophy of the stromal cells which now attain a well-developed cytoplasm for the first time. However, with continued development of the luteal phase the stroma gradually loses its fluid and becomes more dense.[345] Nevertheless, the growth of the endometrial glands more than compensates for the slow shrinkage of the stroma so that the total mass of the endometrium continues to increase.[53]

Concurrently with the development of the epithelial and stromal elements, the endometrial vasculature undergoes significant alterations. The spiral arterioles grow more deeply into the endometrium, almost reaching its surface. In so doing they also become more coiled. Blood flow through new capillary beds, especially around the glands, is promoted.

Within a variable number of days prior to menstruation regressive changes appear in the secretory endometrium. These have been studied in minute detail in the monkey by Markee.[50–53] There is convincing evidence indicating that similar changes, especially in the vasculature, occur in the human.[346] Employing homotransplantation of small pieces of endometrium into the anterior chamber of the eye, Markee was able to visualize the phenomena of menstruation directly. The transplanted grafts behave exactly like the intact endometrium, menstruating at the same time and responding identically to castration and the administration of various hormones. The outstanding developments from this work indicate two important facts. First, that the onset of uterine bleeding is invariably preceded by striking vascular changes. Second, that a *sudden* withdrawal of estrogen or progesterone is an essential prerequisite to endometrial regression.

Collateral experiments indicate that the earliest regressive changes consist in the absorption of edema fluid[345] which tends to diminish the width of the endometrium. This is rapidly followed by an intense leucocytosis, the significance of which is not understood.

The reduced width of the regressing endometrium compromises the spiral arterioles, causing them to be disproportionately long. In accommodating themselves to a narrower endometrium they become more coiled. This results in buckling of the vessels which interferes with the rate of blood flow through them. In addition to reducing the blood supply to the superficial layers of the endometrium, buckling of the arterioles is also followed by stasis of blood near the surface. Okkels[346] has presented evidence suggesting that the opening up of arteriovenous anastomoses at this time permits arterial blood to by-pass the superficial layers. This serves to increase ischemia and venous congestion (stasis) in the superficial portions of the endometrium. The conditions of stasis and ischemia are apparent from one

to five days before bleeding Their combined effect is to produce degeneration of the stromal elements including a weakening of the walls of the arterioles and capillaries Beginning four to twenty four hours prior to bleeding there occurs a striking vasoconstriction of the basal portions *of the spiral arteriole i e those segments* which are situated in the depths of the endometrium and are considerably removed from the layers showing stasis and degeneration Since *constriction of the coiled arterioles preceding* bleeding appears sufficiently intense to result in degeneration and bleeding this has been named as a cause of the bleeding However Markee[5] *has* observed marked degeneration due to stasis prior to the appearance *of* vasoconstriction Nevertheless the ischemic effects of arteriolar vasoconstriction must contribute to the necrobiotic processes already instituted

Vasoconstriction is followed by a temporary relaxation which permits blood to re-enter the *peripheral segments* of the arterioles Since *the walls* of the latter have undergone degeneration they readily burst Small pool *of blood* collect in the *stroma as subepithelial* hematomas These soon penetrate the disintegrating surface epithelium and dark blood slowly streams out over *the surface* These events do not occur *simultaneously* throughout the endometrium Instead one coiled artery after another clamp down then relaxes and leads to bleeding The process is repeated *in different* regions of the endometrium so that menstrual bleeding is spotty and irregular rather than uniform Bleeding from an arteriole is brief and is terminated by vasoconstriction again Constriction of the arterioles before and during bleeding prevents excessive loss of blood *When all the coiled arteries are constricted no bleeding* occurs At the same time the surface of the endometrium is irregularly denuded leaving coiled arteries and glands projecting out *from it*[247] *Blood* also oozes out from veins opened during the sloughing process The blood which courses slowly through the substance of the endometrium does not clot That which is released from the coiled arterioles directly into the uterine cavity without first traversing the stroma undergoes normal coagulation This explains the presence of blood clots in the various menometrorrhagias

During menstruation all of the compact and most of the spongy layer of the endometrium are desquamated The basalis remains intact by virtue of its independent blood supply and acts as a foundation from which new *endometrium can be regenerated* The termination of menstruation is accompanied by the establishment of an adequate circulation The latter develops partly by *dilatation of the straight* arterioles which supply the intact basal layer and partly by the development of a new capillary bed from the *remnants of the coiled* arterioles

Direct visualization of the human endometrium by hysteroscopy just before and during menstruation has yielded data which suggest that the above-described vascular phenomena of stasis and ischemia occur in woman as well as in the rhesus monkey Hasner[247] observed a bluish pale mucosa premenstrually followed by a blanched appearance just before the onset of bleeding Premenstrual pallor of the endometrium was also noted by Schroeder[2 9]

Markee's experiments leave no doubt as to the role of hormones in the *precipitation* of the anatomic changes incidental to menstruation He has

shown that the speed of hormone withdrawal is paramount. A slow decrease in estrogen levels results in slow endometrial regression without bleeding. On the other hand, rapid regression with bleeding follows a sudden decrease in estrogen levels. The effects of estrogen withdrawal can be nullified by the injection of adequate amounts of progesterone which continues to stimulate endometrial growth and prevent its regression. The withdrawal of progesterone which accompanies the waning corpus luteum undoubtedly contributes to endometrial regression. However, it is important to recognize that estrogen withdrawal by itself causes identical regressive phenomena whether or not progesterone had been a factor in endometrial development. Withdrawal of estrogen or progesterone produces the same effects on the circulatory dynamics of the endometrium. However, it is probable that each is effective in a slightly different way. Estrogen withdrawal shrinks the stroma by favoring resorption of edema fluid. Progesterone withdrawal causes involution of the glands which, in time, narrows the stroma. The effect of both of these processes is the same, *i.e.*, buckling of arterioles, stasis, necrosis, vasoconstriction and bleeding.[53] It is thus apparent that there are no qualitative differences in the bleeding at the end of ovulatory and anovulatory cycles. The presence or absence of an actively secreting corpus luteum is not vital to the process of uterine bleeding. Its primary function is that of producing a suitable development of the endometrium in order to provide for implantation of a fertilized ovum.

Despite the clear-cut anatomic correlates involved in the process of menstruation, there is, as yet, no convincing explanation of the mechanisms concerned in their initiation. It is probable that a product of local endometrial catabolism may be the factor which sets off the train of events culminating in menstruation. Olive and George Smith[348,349] have advanced an hypothesis which offers many attractive possibilities. These workers studied the menstrual discharge itself. This was done with the idea that if a "bleeding factor" exists it must originate locally and might be found in the bloody material. As a result of their investigation, a toxic factor was demonstrated in the menstrual discharge as well as in the circulating blood of women during menstruation. This factor has been termed "menstrual toxin" and appears to be identical with a fibrinolytic enzyme associated with the euglobulin fraction, although its chemical nature is unknown. It has also been found by the Smiths in the circulating blood of women with late pregnancy toxemia and during prolonged labor but not in that of nonmenstruating or normally pregnant women. According to their concept the withdrawal of hormonal support results in the formation of tissue catabolites in the endometrium. These, in some unexplained way, cause the release of the menstrual toxin said to be the precipitating cause of menstruation and, incidentally, of late pregnancy toxemia. By a series of immunologic experiments this toxin derived from the breakdown of the endometrium is presumed to be identical with a protein substance released during inflammatory cellular injury. The latter substance was described in pleural exudates induced in dogs by Menkin.[350,351] This has been termed "necrosin" and is regarded as the factor responsible for tissue injury in inflammation. Markee[52] observed constriction of the spiral arterioles of

his endometrial homotransplants following the injection of a necrosin like substance These observations strengthen the concept that tissue catabolism from various causes may result in the release of toxins However much work remains to be done in elucidating the precise mechanisms involved in the initiation of menstruation To date the problem of how hormone withdrawal causes menstruation remains unsolved

Notwithstanding our imperfect knowledge of fundamental mechanisms sufficient data have been accumulated to formulate therapeutic procedures for the induction of menstruation where indicated Even in an individual completely lacking in ovarian function it is possible and at times psychologically desirable to cause periodic bleeding This can be accomplished by the administration of an effective estrogenic hormone in sufficient amount to produce development of the endometrium as described above About three to six days following the sudden cessation of therapy endometrial regression leads to uterine bleeding The time interval between the end of therapy and the onset of bleeding depends on the rapidity with which the body disposes of the estrogen It will be longer with the conjugated natural estrogens When progesterone is employed in conjunction with estrogens the abrupt cessation of therapy is usually followed by bleeding in about forty-eight hours By an appropriate schedule of estrogen therapy such as its continuous administration for twenty-one to twenty two days it is possible to mimic regular menstrual bleeding every twenty five to twenty-eight days

Urinary Hormone Excretion Levels During the Menstrual Cycle —Estrogens progesterone and gonadotropins are excreted in the urine with cyclic variations Because of the limitations inherent in the various methods of assay no accurate statement can be made concerning precise quantitative amounts Nevertheless despite varying reported figures certain general conclusions can be drawn

Estrogens are present in the urine in very small amounts just before during and after the menses Quantities in the range of 10 to 20 gammas or 100 to 200 international units (expressed as estrone) per twenty four hours are present at these times The studies of D Amour [15] and Smith Smith and coworkers [14 15] indicate that there are two peaks of estrogen excretion in the urine during the course of the menstrual cycle The first occurs just prior to ovulation and may reach 800 international units of estrone per twenty four hours This is followed by a fall and then a secondary rise which may be greater or less than the pre-ovulatory peak The timing of the secondary rise is inconstant and apparently coincides with the period of maximum corpus luteal activity

Gonadotropins are present in very small quantities in the urine of normal non pregnant women except at the time of ovulation An ovulatory rise occurred in 25 of the 29 cycles studied by D Amour [15] In general this follows the first peak of estrogen excretion suggesting that the rising titer of estrogens secreted by the maturing follicle is responsible for increased gonadotropin secretion by the adenohypophysis Since urinary gonadotropins are estimated by a variety of different procedures each with a different standard for normal it is impossible to express the findings in uniform terms The fact that a second peak of gonadotropin excretion does not

occur after the second estrogenic peak is probably due to the inhibitory effect of progesterone which is being elaborated at the same time

Pregnanediol is absent from the urine during the follicular phase of the menstrual cycle. According to Venning[311] it rises gradually after ovulation to a peak about the middle of the luteal phase and then falls to very low levels to disappear one to three days prior to menstruation. Since pregnanediol is one of the principal metabolic derivatives of progesterone, its excretion is generally employed as an index of the extent of progesterone secretion by the corpus luteum. The average total amount of pregnanediol excreted during the luteal phase is about 50 mg with a normal range between 30 to 60 mg. At the height of its excretion it may reach 5 to 10 mg in twenty four hours. In Venning's experience the interval of time between the appearance of pregnanediol and the occurrence of menstrual bleeding is fairly constant regardless of the length of the cycle. She has found it to range between eleven and fourteen days. However attention is called to the discordant results reported by Hamblen and his group[323]. These workers found a complete absence of urinary pregnanediol in 13 per cent of patients who bled from a progestational endometrium. On the other hand pregnanediol was demonstrated in the urine of 62 per cent of patients whose endometrial biopsies revealed an estrogenic endometrium (*i e* where no progesterone effect on the uterine epithelium was evident). Furthermore doubt has recently been cast on the assumption that the first appearance of urinary pregnanediol represents previous ovulation. Rogers and Sturgis[35] conclude from correlations between the excretion of free pregnanediol and the basal body temperatures that the former may at times appear prior to ovulation. The possibility of progesterone secretion by preovulatory luteinization of the granulosa and theca cells cannot be excluded in these cases.

Neutral 17 ketosteroids are excreted in the urine of normal non pregnant woman in quantities approximating two-thirds that excreted by the male. Since these compounds in human urine are derived from the adrenal cortex and the male gonads the amount contributed by the latter (about one third of the total) is naturally lacking in the urine of females. The urinary excretion in the female ranges between 5 1 and 14 2 mg per twenty four hours as compared with figures of 8 1 and 22 6 mg for normal men[335]. It undergoes no significant cyclic fluctuation in relation to menstruation[33].

Androgens are excreted by normal women in amounts somewhat less than those excreted by men. Callagher and his coworkers[12] found an average daily urinary excretion of 42 to 56 international androgen units for women and 63 to 68 for men. Each international unit is equal in androgenic activity to 0 1 mg of androsterone. According to Koch[336] there is no significant fluctuation in relation to the menstrual cycle.

PHYSIOLOGY OF OVULATION

In order to avoid unnecessary repetition the hormonal relationships which prevail at the time of ovulation are only briefly restated. As the Graafian follicle matures during the first half (follicular phase) of the menstrual cycle its production of estrogenic hormone gradually increases

This results in increased gonadotropin secretion by the adenohypophysis with a shift in the FSH-LH ratio in favor of the latter at the partial expense of the former. It is generally believed that the rapid outpouring of luteinizing hormone is the immediate precipitating factor in bringing about ovulation. The phenomenon itself has never been observed in the human but has been visualized in rabbits and other mammals.[359,360] It is apparent that it occurs not as a sudden rupture but as a quiet opening of the antral cavity, much as an abscess opens spontaneously.

Following extrusion of the ovum the rent is quickly sealed by a small blood clot and the cavity tends to collapse. Under the continued influence of the luteinizing hormone the lining granulosa and theca cells of the follicle become transformed into lutein cells. In this manner the corpus luteum is formed. While estrogen continues to be secreted, a new hormone, progesterone, is now elaborated as a result of the action of luteotropin. Although ovulation is generally regarded as the dividing point between the purely estrogenic activity of the follicular phase and the mixed secretory activity of the luteal phase, Allen[361] points out that this is not always necessarily true. Experimental evidence is cited to indicate that, at least in some animals, the enlarging follicle may begin to change its secretion toward the progestational type before ovulation actually takes place. Furthermore, follicles which fail to ovulate and therefore contain trapped ova may develop significant degrees of luteinization. Hamblen[33] believes that these considerations may explain certain previously mentioned discrepancies between urinary pregnanediol excretion and evidence of corpus luteal activity.

Data relating to the timing of ovulation have been inclusively summarized by Siegler[343] and by Hamblen.[433] Observations which support the concept that ovulation occurs about the middle of the cycle include the following:

1. The highest incidence of pregnancies resulting from a single coitus at a known time of the cycle occurs when the act takes place between the eighth and nineteenth days.
2. Studies of ovaries and uteri containing very early embryos removed at known times of the cycle have placed ovulation between the thirteenth and nineteenth days. Five human ova have been recovered from the fallopian tubes by lavage on the fourteenth to sixteenth days of the cycle.[462]
3. Confirmatory data have been obtained from studies of peaks in the urinary excretion of gonadotropins and estrogens. Also changes in the electric potential of the uterus have been correlated with the appearance of the ovaries at laparotomy. In certain cases these electrometric studies have revealed electronegativity of the cervix coinciding with ovulation.

Further information relating to the timing of ovulation is often obtainable by noting the day on which intermenstrual lower abdominal pain occurs in some women. This is referred to as ovulational pain or *mittelschmerz* and may be associated with slight uterine bleeding. The simplest and most practical procedures for the timing of ovulation are those which involve a minimum of discomfort and expense to the patient. These include serial studies of the va[illegible]ars and daily basal body temperatures which are

discussed in the following section It is to be emphasized that many procedures are available which provide an approximation of the time of ovulation However we still have no method by which this can be determined precisely

While ovulation in woman characteristically occurs at about the middle of the menstrual cycle, *i e* about the twelfth to fourteenth day of a twenty-eight day cycle, there are many exceptions Ovulation may also occur as early as the eighth and as late as the twentieth day of the cycle[383] From a practical standpoint the determination of the precise day on which ovulation occurs is often not as important as knowing whether or not ovulation occurs at all This becomes a matter of considerable importance in the clinical evaluation of problems of sterility

III CLINICAL RECOGNITION OF THE FUNCTIONING CORPUS LUTEUM

In studies of female infertility ovarian function has been evaluated by the use of basal body temperature charts studies of the cervical mucus and vaginal smears urinary pregnanediol determinations and endometrial biopsies With the exception of the studies dealing with the ability of spermatozoa to penetrate the cervical mucus all these tests are designed to reveal the presence or absence of corpus luteum activity To some extent the results obtained from these tests may also provide a clue as to the adequacy of corpus luteum activity Not only is the secretion of progesterone necessary for proper preparation of the secretory endometrium but it must be present in adequate amounts over a long enough period of time Once such activity has been demonstrated it may be assumed that ovulation had occurred and an adequate corpus luteum had developed Under these circumstances the cause of the infertility must be sought elsewhere

The basal body temperature undergoes cyclic fluctuations during the ovarian cycle Rubenstein [363] and Palmer[364] have shown that the basal temperatures are relatively low during the follicular phase and rise to higher levels during the luteal phase Shortly before menstruation a fall in temperature again occurs Failure of the temperature to fall premenstrually often presages conception The rise in temperature from the relatively low levels to the relatively high levels is usually preceded by a sharp drop The total temperature rise in normal cycles is usually 0 6° to 1 0° F A typical example of a normal temperature record obtained during a menstrual cycle is illustrated in figure 55 The rise may occur rapidly or over a period of a few days It is now generally believed that the rise corresponds to the approximate time of ovulation [384,365,356] although it is not generally known whether this occurs just before during or just after the rise That the elevation of temperature during the luteal phase is due to the secretion of progesterone has been clearly shown by Davis and Fugo[387] and by Buxton and Atkinson [388] The latter workers studied 6 amenorrheic women with little or no endometrial activity and relatively flat temperature curves After preliminary priming with estrogens the subsequent and simultaneous

administration of progesterone invariably resulted in a significant rise of basal body temperature In collateral studies on normal women the administration of chorionic gonadotropin which has a luteotropic effect caused a delay in menstruation and a prolongation of the postovulatory rise in body temperature

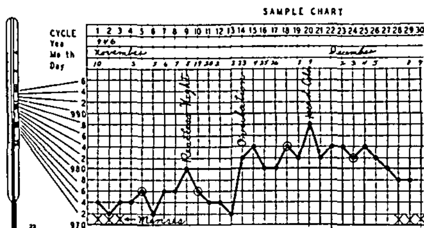


FIG 55 —Example of a typical basal body temperature record obtained during a normal ovulatory cycle (Buxton courtesy of J Clin Endocrin)

If accurate information is to be derived from basal body temperature charts certain precautions must be observed Rectal temperatures must be taken daily before the subject arises from bed Notation should be made of sleepless nights upper respiratory tract infections or other stimuli which may interfere with a true basal reading Specially calibrated thermometers are available which record only 4° F from 96° to 100° These make accurate readings easier to obtain

In studies by the basal body temperature method of 524 apparently normal menstrual cycles in 109 healthy adult women Goldzieher and his associates[365] found that 13 of the cycles were anovulatory and 11 were indeterminate Although the usual length of the luteal phase is generally stated to be from eleven to fourteen days [111] these workers found this duration in only 70 per cent of the cycles The longest luteal phase was nineteen days and the shortest five days Luteal phases lasting less than ten days were noted in 1 8 per cent of the cycles A short secretory phase (less than ten days) or an insufficient temperature rise (less than 0 8° F) *is generally taken to signify inadequate corpus luteum function* This was found by Jones [99] to be the case in 13 per cent of 255 cycles studied in 98 patients complaining of infertility due to endocrine or metabolic causes The temperature records indicated a failure of ovulation in 19 per cent In a report from another sterility clinic Buxton[367] found a short secretory phase in 25 per cent of 127 cycles of 38 patients Endometrial biopsy in these patients showed evidence of unsatisfactory secretory endometrial

development at the time of menstruation This would indicate that patients with a short luteal phase as indicated by basal body temperature records have inadequate corpus luteum function In general it is recognized that the interpretation of temperature records of infertile women is more difficult and less reliable than in fertile women However it is equally apparent that defective corpus luteum function is a statistically significant factor in the etiology of sterility

The determination of urinary pregnanediol excretion has been employed in studies of corpus luteum activity As previously stated pregnanediol is the principal catabolite of progesterone and its appearance in the urine is regarded as an index of progesterone secretion According to Venning[111] it appears at about the time of ovulation reaches a peak urinary excretion about the middle of the luteal phase and then declines in amount so that it is absent from the urine one to three days prior to menstruation The length of time between the appearance of pregnanediol and the onset of bleeding is said by Venning to be fairly constant regardless of the length of the menstrual cycle It usually ranges from eleven to fourteen days The maximum daily excretion may reach 5 to 10 mg in twenty four hours and a total excretion of 30 to 60 mg is generally considered as normal

The absence of pregnanediol from the urine during the second half of the ovarian cycle is generally regarded as indicative of a *failure of ovulation* and corpus luteum formation However attention is drawn to the discrepancies noted by Hamblen and his group[3,3] who failed to detect pregnanediol in the urine of a substantial number of women whose endometria showed a well-defined progesterone effect Further observations of a conflicting nature indicated the presence of urinary pregnanediol in women whose endometrial biopsies showed an absence of progestational development The reason for these discrepancies is not clear but they are important from the standpoint of not depending exclusively on single laboratory procedures in the evaluation of ovarian function

The incidence of low pregnanediol excretion values in a large group of infertility patients was reported by Jones[99] This worker estimated that 34 3 per cent of his patients had deficient corpus luteum function as judged by *a pregnanediol output of less than 4 mg per forty eight hours* at the peak of the luteal phase

Endometrial biopsy is a procedure which is employed to determine the state of endometrial development at the termination of an ovarian cycle Its greatest usefulness lies in its ability to reveal whether or not the endometrium had been stimulated by the corpus luteum hormone It is preferably obtained within the first twelve to eighteen hours after the onset of bleeding Specimens taken after this time may be obscured by extensive endometrial sloughing On the other hand if a biopsy is taken just before the expected time of bleeding a delay in the latter means that the biopsy *does not depict the fullest extent of development attained* at the moment of bleeding

From the degree of endometrial differentiation it is possible to obtain an histologic appraisal of ovarian hormonal function Bleeding can occur from an endometrium in varying degrees of development This may range from the thin senile atrophic type with small sparsely distributed glands to the markedly thickened variety containing a dense stroma and large, di

lated glands of varying sizes This range of endometrial differentiation is due to wide differences in the amount of effective estrogenic hormone At the lower end of the scale is the endometrium found in estrogenic and anovulatory ovarian failure The opposite extreme is characterized by a well marked hyperplasia of the swiss-cheese type such as is seen most often in cases of functional bleeding It is thought to be due to excessive or prolonged estrogenic influences In between is the fully proliferated estrogenic endometrium which is normally present at the end of the follicular phase of ovarian cycles Its presence at the beginning of a period of uterine bleeding indicates an absence of corpus luteum development and therefore anovulatory bleeding

The presence of a mature progestational endometrium is readily recognized by the marked secretory development of its glands These are enlarged and twisted and present characteristic alterations of their epithelial cells They become taller and the presence of subnuclear vacuoles attests to their heightened secretory activity These are due to deposits of glycogen and mucin As this stage attains maximum development the cellular vacuoles migrate to the distal portions and ultimately discharge their contents of glycogen and mucin into the glandular lumens When this type of endometrium is found at the onset of bleeding an adequate progesterone secretion from an active corpus luteum can usually be taken for granted Inadequate progesterone effects can be recognized in various types of mixed endometrial development In these the competent cytologist differentiates scattered areas which are due to the influence of progesterone A further evidence of inadequate luteal activity is the presence of progestational development which has not developed beyond an immature stage This is the type of endometrium which is commonly associated with the short luteal or secretory phase described above and recognized by basal body temperature records

The vaginal smear is occasionally useful in the evaluation of corpus luteum activity Papanicolaou [8] first demonstrated the presence of cyclic changes in the vagina of normally menstruating women Based on his observations several methods have been applied to the study of ovarian function by examination of serial smears of exfoliated vaginal epithelial cells In our experience the simplest least time-consuming and most informative method is that of Shorr[366] who devised a modified Masson trichrome stain The various dyes are incorporated in a single differential stain which renders sharply contrasting colors to the epithelial cells depending on their state of estrogenization The effect of estrogens on the vaginal epithelial cells is to produce cornification This is readily recognized not only by the large flat wafer like contour of the cell but by its pink color Non-cornified cells take on a greenish blue color which easily distinguishes them from the mature cornified elements

Estrogenic influences are recognized in stained smears with great facility even in the hands of the inexperienced worker Because of this it is quite easy to estimate the day to-day estrogenic activity in the given subject Shorr and his collaborators[322, 368] have demonstrated a sharp peak in the extent of vaginal cell cornification at the time of ovulation That the peak in cornification occurs at about the time of ovulation has been confirmed by a direct correlation with the mid-cycle rise in basal body temperature [339]

However, since a peak in cornification merely represents an estrogenic effect it does not necessarily prove the existence of ovulation. For example, it can be detected occasionally in anovulatory cycles. Under these circumstances however other cytologic characteristics of the smears (the presence of immature deep cells and the very low incidence of cornification at other stages of the cycle) may indicate its non-ovulatory character.



See opposite page for legend

While the recognition of estrogenic effects is fairly simple this is not true for the evaluation of the effects of progesterone during the luteal phase. This often proves to be difficult and uncertain even in the hands of the experienced cytologist. The decline of cornification clumping of cells and wrinkling folding and curling of their edges are said to be characteristic of the progestational phase. The absence of these features in the frankly anovulatory cycle especially when associated with the presence of immature cells derived from the deep layers of the vaginal mucosa is indicative of ovarian failure and is readily recognized. The principal diagnostic difficulty lies in the evaluation of the border line cases where estrogen secretion is present but luteal activity is uncertain. In these instances the use of basal body temperature records in conjunction with endometrial biopsy studies proves most valuable.

It is to be emphasized that the proper use of the vaginal smear technic necessitates daily or almost daily examinations. The patient can be instructed to take the smears herself place them in the fixative and bring them as a group to the laboratory. Single observations are wholly inadequate because of the abrupt changes in vaginal cytology which may be noted from day to day. Significance can only be attached to serial smears from which the general trend of hormone fluctuations may be detected.

PHYSIOLOGY OF PREGNANCY

Gestation represents the ultimate in the realization of the reproductive functions of the ovaries. What has been said in the foregoing sections applies principally to the normal physiology of the sexual cycle in the non pregnant, regularly menstruating woman. Fertilization of an ovum followed by its implantation into the progestational endometrium interrupts the usual reproductive cycle and introduces a new and elaborate system of complex physiological and hormonal interrelationships.

LEGEND FOR FIGURE 56

FIG 56 —Vaginal smears during various phases of a normal menstrual cycle. The black and white illustrations do not portray the sharp color differentiation between pink cornified and blue-green non-cornified epithelial cells. However cornified and non cornified cells can be distinguished by their morphologic characteristic. The former are mature large wafer like cells with small pyknotic nuclei. The younger non cornified cells are smaller in size but have larger nuclei. (Shorr Single Differential Stain Multichrome Clay Adams Co Inc Dr Ephraim Shorr New York Hospital Cornell University Medical Center)

A Postmenstrual phase 4th day. Cornification is minimal. There is considerable desquamation and mucus.

B Early pre-ovulatory phase 10th day. About one-half the cells are cornified. They are more discrete and the mucus is thinner.

C Ovulatory peak 13th day. The smear is characteristically clean with very little mucus and no leucocytes. The majority of cells are cornified.

D Postovulatory reaction 14th day. Within 24 hours of ovulation the appearance of the smear is markedly altered. Many leucocytes are evident and cornification is reduced. The epithelial cells are clumped wrinkled and show folding of their edges. Mucus is thicker.

When fertilization takes place it occurs within twenty four hours after coitus. Penetration of the ovum by the spermatozoon takes place in the fallopian tube within a matter of several hours after the former has been extruded from the ovary. It generally requires about two or three days for the fertilized egg to reach the uterine cavity where it spends another five or six days before becoming implanted in the endometrium. Hertig and Rock[30] searched for early eggs in uteri removed at operation and found one estimated to be seven and one half days old. It may therefore be assumed that the human egg is implanted on about the seventh or eighth day after fertilization. Since ovulation usually occurs on about the fourteenth day of a twenty-eight day cycle, nidation therefore is accomplished by about the twenty-second or twenty third day or about five to six days *before the expected menstrual flow*. At this time the endometrium has attained a maximum progestational differentiation under the combined influence of estrogen and progesterone.

Where as failure of ovum fertilization leads to corpus luteum degeneration, endometrial regression and menstruation, the opposite event results in further differentiation of the endometrium. The progestational endometrium is gradually and imperceptibly transformed into the decidual type. It is now characterized by three layers which are even more distinct than they were in the well developed secretory endometrium. The deepest zone adjacent to the myometrium is known as the *decidua basalis*. The intermediate spongy layer is occupied by markedly hypertrophied and convoluted glands. The superficial or compact layer contains relatively few glands but the stromal cells in this region have now acquired a wide area *of cytoplasm and are known as decidual cells*. These cells are large and polygonal and are arranged in a pattern resembling a mosaic. Where the superficial layer overlies the early embryo it is known as the *decidua capsularis*; elsewhere it is termed the *decidua parietalis*. As the embryo grows the expanding capsular decidua fuses with and absorbs the adjacent parietal portion. At the third month fusion of the capsular and parietal layers is complete on all surfaces so that the uterine cavity is obliterated.

Even before the early decidual changes appear in the endometrium the *fertilized ovum has undergone developmental changes during its tubal* and intra uterine sojourn. Cell division has taken place and a central vesicle has appeared so that the early embryo (morula) is now spoken of as a blastocyst. It is lined by a layer of cells known as the primitive chorion. Shortly before implantation the smooth chorionic surface develops polypoid projections which are called trophoblastic buds. At first these are solid but are later penetrated by a central core of mesenchymal tissue to form the *chorionic villi*. The cells of the latter soon differentiate into two distinct layers which constitute the *trophoblast*. The inner layer is referred to as the *cytotrophoblast* which comprises a trophoblast shell, cell columns, cell islands and the *Langhans cells*. Externally is a mass of tissue lacking cellular definition and known as the *syncytial trophoblast*. It is secondarily derived from the cellular trophoblast which it gradually replaces as the implanted embryo thrives in its endometrial environment.

The trophoblast which is derived from the chorionic epithelium gives rise to the placenta. It provides for the nutrition of the embryo by the

invasion and absorption of the uterine decidua. Metabolites from the maternal blood circulating in the intervillous spaces are readily available to the embryo by *absorption through the trophoblast. Contrariwise fetal* waste products are excreted through the trophoblast. It is believed that the parasitic growth of the embryo and the transfer of metabolites is mediated by a variety of enzymatic and chemical processes. These have been studied histochemically by Wislocki, Dempsey and Fawcett[373] who adduce evidence that the trophoblast secretes proteolytic and cytolytic enzymes. These workers also present data indicating that the cytotrophoblast produces *chorionic gonadotropin* while the syncytial *component elaborates* steroid hormones.

Endocrine Function of the Placenta.—Having traced the development of *the placenta it is now appropriate to turn to a consideration of its endocrine* function. Evidence substantiating the secretory activity of the placenta in relation to the production of estrogens and progesterone was presented in previous sections dealing with the sites of origin of these hormones. In addition to the isolation of large amounts of derivatives of these steroidal hormones from the urine of pregnant women, the active principles themselves have been recovered in large quantities from placental tissue. Moreover, it has been repeatedly demonstrated that pregnancy can continue uninterruptedly when the corpus luteum is removed from the ovary, even during the first month[372] or before the first missed period.[373] The con*tinued urinary* excretion *of pregnanediol under these circumstances* indicates that the corpus luteum is not only not essential for the maintenance of pregnancy but that it is not the only site of progesterone secretion. More important *is the fact that both ovaries may be removed during the* early months without affecting the outcome of gestation.[311, 406] A transient decline in the urinary excretion of estrogens is occasionally observed but this *is followed* by the usual rise in estrogen and pregnanediol excretion characteristic of the later months.[311] These observations, together with the fact that the removal of the placenta results in a sharp decrease in hormone excretion, indicate that the placenta supplants the function of the ovaries, especially the corpus luteum, in the maintenance of pregnancy. The hormonal activity of the chorio-placental system begins directly after implantation of the embryo. It progressively usurps the function of the ovaries in the secretion of estrogen and progesterone. Between the second and third months the placenta replaces ovarian secretory activity entirely. Thereafter the ovaries show gross and histologic evidence of physiologic regression. Follicular maturation is suspended as a result of adenohypophyseal suppression by increasing amounts of estrogen and progesterone formed by the placenta. The corpus luteum of pregnancy persists longer than the *corpus of menstruation* as a result of stimulation by *chorionic* gonadotropin but shows signs of degeneration after the third month. During the third and fourth months the placenta shows signs of increasing secretory activity. This is the time when the urinary excretion of estrogens and pregnanediol begins to rise.

Chorionic Gonadotropin.—In 1927, Aschheim and Zondek[14] demonstrated the *presence of unusually* large amounts *of* gonadotropin in the urine of pregnant women. At first it was thought that this substance represented

only an overflow due to an overactive pituitary. However Collip[375] soon proved the placenta to be the site of its elaboration. Further confirmation lay in the demonstration by Evans and Simpson[376] that although the adenohypophysis is enlarged during pregnancy its gonadotropic potency is not increased. In fact, later work showed that adenohypophyseal gonadotropic function during pregnancy is reduced or absent. This has been shown to be true for humans[396] as well as for animals. Further evidence of a direct nature to prove the formation of pregnancy gonadotropin by the placenta was presented by Jones, Gey and Gey.[377] These workers assayed the later generations of new cells obtained by *in vitro* cultures of placental cells and found gonadotropic responses in immature rats. Recent tissue culture studies of the human placenta confirmed the elaboration of gonadotropin by these cells.[380] Hormone production appeared to be correlated directly with the growth of Langhans cells. Once the origin of the pregnancy type of gonadotropin was definitely established to be the placenta and not the pituitary it became known as the *chorionic gonadotropin*. Its physiologic effects on the ovary indicate that it consists principally of a luteinizing factor. In this respect its effect is remarkably similar to that of the LH principle of adenohypophyseal gonadotropin.

Following conception and implantation chorionic gonadotropin appears in the urine almost immediately. The urinary excretion of this hormone provides the basis for several pregnancy tests (Aschheim Zondek, Friedman). By and large these depend on the ability of hormone-containing patient's urine to induce gonadal changes in immature test animals such as the rabbit, rat or mouse. So rapidly does the chorionic gonadotropin appear in the urine that a diagnosis of pregnancy may occasionally be made even before a menstrual period has been missed.[378]

As previously mentioned chorionic gonadotropin is produced by the cellular component of the trophoblast. Its principal function is to stimulate the corpus luteum and thereby favor its continued secretion of estrogen and progesterone. In this way the formation of the uterine decidua is promoted. The action of human chorionic gonadotropin on the human ovary has been expounded recently by Brown and Bradbury.[400 401] These workers demonstrated its luteotropic activity by showing its ability to produce pseudo-pregnancy in normal women. This state was recognized by delayed menstruation, endometrial biopsies showing decidual changes, a prolonged urinary excretion of pregnanediol and a positive pregnancy test in the urine (Aschheim Zondek).

The curve of urinary gonadotropin excretion during pregnancy has been studied by Browne and Venning[379] and has been recently summarized by Venning.[111] Chorionic gonadotropin first appears in the urine about the time of nidation, usually the twenty fifth day of the cycle. The quantity increases at a rapid rate reaching a maximum about fifty to seventy days after the beginning of the last actual menses. The height of the peak varies in different subjects ranging from 40 000 to 200 000 rat units per twenty four hours. Within a short time, usually a few days, the rate of excretion rapidly decreases. By approximately the one hundred tenth to one hundred twentieth day between 5000 and 10 000 rat units are excreted daily. From this time until the termination of pregnancy the urinary levels re-

main fairly constant ranging between 1000 and 10 000 rat units per day Atypically a secondary but temporary rise in urinary gonadotropins has been observed in a few normal subjects during the last trimester A similar secondary rise in urinary and serum gonadotropins may also occur in patients with late toxemia of pregnancy[391,392] After parturition, urinary gonadotropins fall to their prepregnancy levels within three to ten days The curve depicting the urinary excretion of chorionic gonadotropin in normal pregnancy is illustrated in figure 57

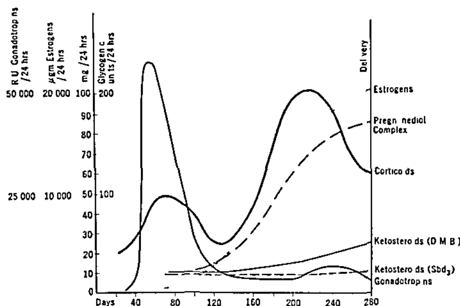


Fig 57 —Excretion curves of chorionic gonadotropin estrogens pregnanediol complex corticoids and ketosteroids during normal pregnancy (Venning[11] Normal and Pathological Physiology of Pregnancy courtesy of Williams and Wilkins)

The curve of gonadotropins in the blood during pregnancy has been studied[376,381] and found to parallel that of the urinary excretion

It is important to recognize that the urinary excretion of chorionic gonadotropin signifies only the presence of functionally active chorio placental tissue Therefore it gives no information as to whether the pregnancy is uterine or extra uterine or whether the fetus is alive or dead Not until the placenta is completely detached or disintegrated does the chorionic gonadotropin disappear from the urine Furthermore similar and even larger amounts of an identical hormone may be excreted in the presence of certain tumors derived from chorionic tissue i e chorionepithelioma and hydatidiform mole in women and chorionepithelioma in men

Estrogens —The elaboration of estrogens by the placenta has been discussed in a previous section It remains now to examine the urinary excretion of these substances during the gestational cycle In the earliest stages estradiol estrone and estriol are excreted in amounts only slightly

greater than those found during the menstrual cycle. Usually between the sixtieth to eightieth day after the last menstrual period the urinary excretion of estrogens begins to rise. This occurs on the average, about a week or two after the peak of urinary gonadotropin has been passed. The rise becomes quite sharp and rapid after the one hundredth day and may in some cases reach values from 40 000 to 50 000 micrograms per twenty four hours.[111] The marked increase in the estrogenic content of pregnancy urine is due almost entirely to a great increase in the estriol fraction. Estradiol and estrone increase but slightly. The general trend in the urinary excretion of estrogens is illustrated in figure 57. According to Venning[111] estrogens continue to rise up to the time of delivery. On the other hand Smith and her coworkers[393] observed an abrupt fall several days before parturition. It is not clear whether differences in assay technics are responsible for this discrepancy. A progressive fall in the urinary excretion of estrogens (and pregnanediol) several weeks before term is regarded by the Smiths[39] as an indication that late toxemia of pregnancy is imminent. They find this to be an especially reliable omen when there is an associated increase in the urinary excretion of chorionic gonadotropin. Cohen and his colleagues[394] showed an interesting alteration in the chemical state of the estrogens which occurs shortly before term in the normal gravid woman. Until this time approximately 99 per cent of urinary estrogens is in the biologically inactive form conjugated with glucuronic acid. Just before or during labor this situation is reversed so that estrogens are now present principally in the free non-conjugated state.

Pregnanediol – Studies of the urinary excretion of this substance during pregnancy reflect the increasing secretion of progesterone. Venning's[111] observations have been confirmed by others.[2,3] Instead of the premenstrual fall noted in the absence of conception pregnanediol continues to be excreted in the urine in the amounts characteristic of the luteal phase or slightly higher. Between the sixtieth and ninetieth days a definite rise in urinary excretion occurs corresponding to the beginning rise in estrogen excretion. Thereafter there is a gradual increase throughout pregnancy which parallels the rise in estrogens. At term most values lie between 50 and 100 mg per twenty four hours as determined by Venning's gravimetric procedure. Following delivery and separation of the placenta pregnanediol rapidly disappears from the urine. The curve of urinary excretion of pregnanediol during pregnancy is set forth in figure 57. Venning[111] and others[40] have not observed the marked decrease in pregnanediol output prior to the onset of labor described by some investigators.[233 393 403]

Adrenocorticotropin —Recent studies by Jailer and Knowlton[409] suggest that the placenta may elaborate an adrenocorticotropin. These workers demonstrated its presence in the placental tissue of a patient with Addison's disease. It remains to be determined whether this adrenocorticotropic substance is actually formed in the placenta or merely stored there after being produced elsewhere.

The Urinary Excretion of Adrenocortical Hormones During Pregnancy — The study of the excretion of urinary metabolites of the hormones of the adrenal cortex has been the subject of considerable investigation by Venning.[111 396] Two groups of adrenal metabolites were studied the neutral

17-ketosteroids and the corticoids. The former are considered to be associated with adrenal androgenic function while the second group of substances affect carbohydrate and protein metabolism.

Figure 57 shows the curves of urinary excretion of the adrenocortical metabolites as obtained by Venning in 9 pregnant women. An increased excretion of corticoids occurs during the first trimester but soon returns to normal. A secondary rise is again noted between the one hundred fortieth and one hundred sixtieth days. In some cases it reaches values over 300 glycogenic units as determined by the method of Venning, Kazmin and Bell.[397] A slight decrease is usually observed in the latter part of pregnancy although the amount is still well above normal. It is of interest but unclear significance that the first peak of corticoid excretion coincides with that of gonadotropin excretion. The second peak occurs simultaneously with the sharp rise in urinary estrogens and pregnanediol. The presence of increased adrenocortical activity during the latter months of pregnancy is consistent with the knowledge that adrenal cortical hypertrophy occurs at this time. However, it should be noted that an increased urinary excretion of the glycogenic corticoids (neutral reducing lipids) has been recorded in the pregnant Addisonian patient.[402] This suggests an extra-adrenal source of adrenocortical-like hormones.

In striking contrast to the significant changes in corticoid excretion during gestation are the relatively constant values of urinary neutral 17-ketosteroids. This is true only when the antimony trichloride method of Pincus[395] is employed for the determination. This procedure excludes 20-ketosteroids, one of which (pregnanolone) is excreted in large amounts in pregnancy urine. The excretion of this compound accounts for the increased quantities of ketosteroids detected during the second half of pregnancy when the Zimmerman reaction is used since this color reaction measures 20- as well as 17-ketosteroids.

Dobriner and his associates[399] have studied the ketosteroid components in the urine of pregnant women. They find that these differ qualitatively as well as quantitatively from those normally present in the urine of non-pregnant women. As a result of their studies 11 new ketosteroids were isolated. These occur only in human pregnancy urine and bring the total of ketosteroids found in pregnancy to 19. The 5 previously known ketosteroids occurring in the urine of pregnant women are: isoandrosterone, androsterone, pregnanol-3(α)-one-20, allopregnanol-3(α)-one-20 and allopregnanol-3(β)-one-20. Three ketosteroids were found both in the urine of pregnant women and of normal subjects. These are: Δ^2-androstenone-17, Δ^{3-5}-androstadienone-17 and etiocholanol-3(α)-one-17.

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if not impossible, to classify all clinical syndromes of ovarian dysfunction in terms of hyperfunction or underfunction In general however many ovarian disorders especially those characterized by marked variations in uterine bleeding and changes in secondary sex characteristics can be definitely correlated with functional deficiencies or excesses From a nosologic point of view categorization of ovarian dysfunction along etiologic lines contributes to a better understanding of clinical disorders However causative factors are often poorly understood so that it is more practical to classify and discuss ovarian endocrine diseases according to their most prominent clinical manifestations Wherever possible, established etiologic and pathologic entities will be correlated with endocrine disturbances but for the most part the text of the present discussion is based on groupings of clinical symptoms rather than on specific diseases This is the approach favored by most clinicians

It is important to recognize at the outset that manifestations of disturbed ovarian function may be due to primary ovarian causes or they may be secondary to extragonadal factors Because of the dominant role played by the adenohypophysis in the regulation of ovarian function the latter is readily affected by disordered states of the anterior pituitary These in turn may be due to intrinsic disease in or near the pituitary or may be the result of remote morbid processes which secondarily modify the gonadotropic activity of the adenohypophysis

The vast majority of clinical conditions under discussion are characterized by decreased ovarian function A much smaller group is distinguished by evidences of increased function of the ovaries These include instances of true precocious puberty which have been discussed in a previous chapter They are characterized by the premature development in a child of a full complement of adult ovarian functions including follicle maturation ovulation corpus luteum formation menstruation and the appearance of sexual and somatic maturity The remaining diseases which produce evidence of increased ovarian function are those which result in heightened estrogen secretion These include two entirely different conditions The first is a persistence of one or more actively secreting Graafian follicles causing a type of functional uterine bleeding known as metropathia hemorrhagica The second is a special type of ovarian tumor (granulosa cell and theca cell) which is capable of increased estrogen secretion This and other ovarian tumors having endocrine effects upon the organism are discussed at the end of this chapter p 662

Hypoovarianism —Several types of female hypogonadism are recognized in clinical practice These vary according to the nature and extent of the deficiency of the individual functions of the ovary Arranged in an ascending order of severity three major groups of ovarian hypofunction can be differentiated These are corpus luteum deficiency anovulation and estrogen failure All of these conditions may produce characteristic menstrual disorders which are often the first reason compelling the patient to seek medical attention

Corpus Luteum Deficiency —Included in this group are those instances in which ovulation and corpus luteum formation occurred but luteal secretory activity is defective There are no overt endocrine or somatic mani

Chapter 20

DISEASES OF THE OVARY

Hypoovarianism. Corpus Luteum Deficiency. Anovulatory Failure. Estrogenic Failure. Problem of Delayed Adolescence. Hypoestrogenic Osteoporosis. Estrogen and Gonadotrophin Therapy. Climacteric Syndrome of Ovarian Agenesis. Panhypopituitarism. Relative Hypopituitarism. Functional Uterine Bleeding. Feminizing and Masculinizing Tumors of the Ovary. Virilism and Nontumorous Ovarian Disease.

By Arthur R. Sohval, M.D.

Introduction.—Not all forms of ovarian disease are accompanied by endocrine disturbances. There are many congenital, inflammatory, cystic, degenerative and neoplastic diseases of the ovary which cause no disorders of endocrinologic significance. This is principally because of confinement of the pathologic lesion to a single ovary. Under these circumstances, the uninvolved gonad is capable of maintaining adequate function. However, these diseases do produce hypoovarianism when there is bilateral involvement of sufficient extent to compromise the functions of internal secretion. It must be noted, however, that unilateral disease does result in endocrine manifestations in certain instances of hormone-producing tumors and persistent Graafian follicles. These disorders are characterized by excessive rather than deficient hormone secretion.

The clinical manifestations of disturbed ovarian function are readily divisible into three major groups based on the principal functions of the normal ovary. These include the production of ova and the elaboration of the two ovarian hormones, estrogen and progesterone. As with most glands of internal secretion, ovarian dysfunction may be characterized by an excess or deficiency of one or more of its constituent activities. So closely interrelated are the individual gametogenic and secretory functions of the ovary that a disturbance of one is often, but not necessarily always, accompanied by a disorder of the others. Furthermore, involvement of the separate functions of the ovary may parallel one another in the direction of hypofunction or may be distinguished by excessive activity of one function in association with depression of another. For example, gametogenic failure (anovulation) may be associated with total secretory failure in some cases, while in others it may be accompanied by evidences of normal or increased estrogenic activity. On the other hand, estrogenic failure is invariably associated with anovulation and absence of progesterone formation. A disturbance in corpus luteum function may be the sole manifestation of ovarian dysfunction while ovum formation and estrogen production remain intact.

From a mathematical consideration of the various combinations in which disturbed ovarian function may present itself, it is obvious that the possibilities are several. In the light of present knowledge it is impractical

Deficient corpus luteum activity requires no therapy unless it is a factor in the causation of sterility or early abortion Browne and Venning[3] have shown that chorionic gonadotropin * derived from human pregnancy *urine stimulates the function of the human corpus luteum* *Progesterone* secretion is increased as evidenced by an increased urinary excretion of pregnanediol and its utilization by the endometrium is enhanced Although Siegler[6] could not confirm these results *Hamblen[7] was successful* The latter author has outlined a course of therapy which appears to be effective in some cases Chorionic gonadotropin is employed when deficient progesterone *secretion* is thought to be due to decreased adenohypophyseal gonadotropic stimulation The hormone is administered intramuscularly in daily doses of 500 international units from the fifteenth day of the menstrual cycle until the onset of menstruation *Therapy is discontinued if* bleeding occurs Treatment should be resumed in a similar manner for 3 or 4 additional cycles or until it is felt that it is ineffective as determined by studies of the basal body temperature *record* and vaginal smears

When it is thought that intrinsic ovarian factors are contributory Hamblen[7] recommends the simultaneous administration of estrogen and progesterone during the second half of the menstrual cycle The former may be given orally as diethylstilbestrol 3 mg estrone sulphate 3 75 mg or ethinyl estradiol 0 3 mg daily Progesterone may be administered intramuscularly in the crystalline form 5 mg daily or as the orally effective anhydrohydroxyprogesterone 40 mg daily

Anovulatory Failure – This is a somewhat more advanced form of ovarian deficiency than the isolated corpus luteum failure just described Follicle maturation usually occurs but the enclosed ovum is not discharged and consequently there is no corpus luteum formation There are no external manifestations although sterility is the absolute rule Periodic uterine bleeding often occurs at regular intervals and even when irregular it is usually indistinguishable from true menstruation Anovulatory bleeding is physiologic at the extremes of woman s reproductive career *i e* at the menarche and just before the menopause Anovulation itself is also physiologic during pregnancy and the puerperium

It is generally believed that anovulatory menstrual cycles occasionally occur during the active reproductive life of normal women[8,9] They are apparently quite rare in women whose periods are regular[10] Although there are usually no endocrine manifestations associated with anovulatory failure there may at times be periods of amenorrhea interrupted by episodes of uterine hemorrhage The latter is a type of functional uterine bleeding known as metropathia hemorrhagica and is discussed in a later section The hormonal mechanisms involved in this special type of ovula-

Chorionic gonadotropin has been derived from human pregnancy urine placenta and pregnancy serum Its biologic properties were described in the preceding chapter and consist primarily of luteinizing and luteotropic effects on the ovary Its potency is expressed in terms of the international unit which has been adopted by the Health Organization of the League of Nations as a standard of reference One international unit of this gonadotropin prepared from human pregnancy urine is equivalent to 0 1 mg of the international standard powder This quantity exerts the minimum activity required to cause vaginal cornification in the immature rat

festations other than short menstrual cycles (polymenorrhea or hypermenorrhea) This condition may account for sterility or infertility in the form of early abortion

Defective luteal function may be characterized by an inadequate secretion of progesterone or by an abnormally short period of activity It is encountered most frequently among sterility patients where its incidence has been estimated to range from 13 per cent of 255 menstrual cycles studied[1] to 25 per cent of 127 cycles No figures are available concerning its actual incidence in the general population

When this condition is suspected its existence can be surmised or determined in the following ways

1 Basal body temperature records may show a period of less than ten or eleven days between the dip and sharp rise at ovulation and the onset of menstruation This phase should normally last eleven to fourteen days

2 Serial vaginal smears may also indicate a short and inadequate luteal phase *Like the curve of basal body temperatures a sharp transition occurs* at the time of ovulation This is recognized by a marked increase in the number of cornified epithelial cells followed within a matter of hours by a sudden outpouring of leucocytes into the vaginal secretion The recognition *of ovulation less than ten days before the menstrual flow indicates a* shortened phase of luteal activity More difficult to evaluate but helpful at times is the cytologic evidence of inadequate progesterone secretion This may occur during a phase of normal duration and can be recognized by the presence of desquamated sheets of vaginal epithelium and the absence of clumping folding and curling of individual cells which are normal characteristics of the secretory phase[3]

3 Studies of the urinary excretion of pregnanediol may provide confirmatory data Since this substance is the chief metabolic end product of progesterone its urinary excretion serves as an index of progesterone secretion An excretion of less than 2 to 3 milligrams per twenty four hours or excretion during an abnormally short period of time is highly suggestive As with the basal body temperature and vaginal smear methods of study, pregnanediol determinations should be done serially Because of the low amounts normally present it is often advisable to have assays on forty eight hour urine specimens These should start at the time of ovulation as indicated by the basal body temperature record or vaginal smear studies and should be continued until menstruation begins

4 Endometrial biopsy obtained just before or within twelve or eighteen hours after the onset of menstruation reveals the degree of differentiation induced by estrogen and progesterone Following a normal ovarian cycle characteristic secretory (progestational) changes will be present The presence of an estrogenic or a mixed immature progestational endometrium indicates an absent or deficient progesterone effect respectively The former type of endometrium is normally present at the time of ovulation and its persistence through the remainder of the cycle indicates an absence of progesterone effect Mixed types or areas of both estrogenic and progestational development are normally present early in the secretory phase and their persistence usually signifies a deficiency of progesterone effect This type of endometrium is also known as irregular ripening[4]

fourth day. Diethylstilbestrol 3 mg, estrone sulphate 3.75 mg, or ethinyl estradiol 0.3 mg may be employed. Progesterone is administered from the fifteenth to the twenty-fourth day. This may be given as intramuscular injections of progesterone 5 mg daily or 10 mg every other day, or as anhydrohydroxyprogesterone orally in 40 mg daily doses. Regardless of the previous regularity of uterine bleeding, bleeding usually occurs within three to five days after the cessation of treatment. If bleeding occurs during therapy, treatment should be discontinued and another cycle of therapy begun on the fifth day after bleeding started. Hamblen and his coworkers[11] have found that the cyclic administration of estrogen and progesterone in this manner resulted in the initiation or return of normal ovarian function in a substantial number of young women. If the clinical course and laboratory tests show no results after 2 or 3 such cyclic courses of therapy, a trial with gonadotropins is indicated. This is particularly true when a lack of pituitary gonadotropic stimulation is suspected.

The use of gonadotropins is withheld until cyclic estrogen-progesterone therapy proves ineffective. This is because of the frequency of disturbing allergic reactions. The administration of gonadotropins should be preceded by skin tests for this reason. Two different types of gonadotropins are employed in order to obtain both the follicle-stimulating and luteinizing effects. Equine gonadotropin* is given for ten days from the fifth to the fourteenth day of the cycle. It is administered as daily intramuscular injections in doses of 400 international units each for its follicle-stimulating effect. This is followed by another ten days of treatment with chorionic gonadotropin from the fifteenth to the twenty-fourth day. It, too, is given as daily intramuscular injections in doses of 500 international units each for its luteinizing effect. The occurrence of bleeding during therapy is an indication for stopping the injections. This method of cyclic administration of two different gonadotropic preparations is designed to imitate the type and sequence of gonadotropic stimulation to which the ovaries are normally subjected.

Hamblen and his associates[12] have reported that more than 50 per cent of young women with anovulatory ovarian failure respond to this treatment with the production of a secretory endometrium. Endometrial biopsy is required to demonstrate this effect and if it is obtained in a given case further therapy is withheld until after an adequate trial of attempted conception. In the absence of a demonstrable effect, such effect being indicated by a positive biopsy or actual pregnancy, a cycle is permitted to pass without therapy. The course of cyclic gonadotropin therapy is then repeated using twice the previous doses after preliminary skin testing. If a negative response is now obtained the ovaries are judged to be refractory and further

* The equine gonadotropin is secreted by the placenta of the pregnant mare and is unique in that it is not excreted in the mare urine although it is abundantly present in the serum. Its properties are dissimilar from either pituitary or chorionic gonadotropin but its biologic actions resemble a combination of both FSH and LH, predominantly the former. According to the standards adopted by the Health Organization of the League of Nations 1 international unit is equal to 0.25 mg of the international standard powder. Twenty international units are approximately equivalent to 1 Cortland Nelson unit.

tory failure and bleeding are presumably based on a continuous, high secretion of estrogen by one or more persistent Graafian follicles which have failed to ovulate. The hormonal basis for anovulatory cyclic bleeding has been discussed in the previous chapter, p. 559. It is undoubtedly related to estrogen withdrawal resulting from atresia of the unruptured mature follicle.

The causes of anovulatory failure in the absence of associated hypoestrogenism are unknown. From our knowledge of the physiologic factors involved in normal ovulation it may be presumed that the adenohypophysis may be at fault in supplying FSH and LH in an improper ratio. It is also possible that intrinsic ovarian factors may account for a lack of responsiveness to the hormonal stimuli for ovulation.

Anovulatory failure usually passes unrecognized unless the patient seeks medical attention because of sterility or abnormal uterine bleeding. The diagnosis can be suspected by employing the various laboratory aids discussed in connection with defective corpus luteum activity. Basal body temperature records fail to reveal the mid-menstrual dip and rise characteristic of ovulation. Serial studies of the vaginal smears usually disclose an absence of the sharp peak in cornification of the epithelial cells which accompanies ovulation. Caution must be exercised in evaluating an intermenstrual peak which occurs merely as a result of estrogen elaborated by the maturing follicle. This occurs independently of ovulation and is usually not as marked or characteristic as when ovulation actually occurs. Furthermore, it is apt to occur a few days prior to bleeding rather than at the midpoint of the cycle. No or very little pregnanediol is excreted in the urine, indicating a failure of corpus luteum development consequent upon anovulation.

An absolute diagnosis of anovulatory failure depends, of course, on the demonstration at laparotomy during the premenstrual phase of a complete absence of corpora lutea from the ovaries. Since this is rarely feasible, reliance may be placed upon indirect evidence obtained from a study of endometrial biopsy material. Instead of the progesterone induced secretory endometrium expected at the time of bleeding, one finds only the proliferative or estrogenic type. At times poorly differentiated progestational changes may be found in some areas of the endometrium. These are attributable to small amounts of progesterone secreted by abortive areas of follicle luteinization which may occur in the absence of ovulation.[7]

As with other minor degrees of ovarian hypofunction, anovulatory failure requires no therapy unless it be for the purpose of overcoming sterility or the excessive bleeding of metropathia hemorrhagica. For anovulatory sterility, treatment is directed against probable intrinsic ovarian or hypogonadotropic factors. This is accomplished by a treatment program designed to mimic the normal hormonal milieu which prevails throughout a menstrual cycle. Hamblen[7] has devised a schedule of therapy in accordance with these principles which consists of cyclic estrogen progesterone administration followed if necessary by the cyclic administration of gonadotropins.

Counting the first day of the cycle as the first day of the menstrual flow, estrogen is administered daily orally from the fifth through the twenty-

or by supplying appropriate gonadotropins exogenously In the event that ovarian function is not initiated in this way, recourse to estrogen replacement therapy is then necessary

Differentiation between primary and secondary ovarian hypofunction is most reliably made by determining the urinary content of gonadotropins Adult patients with intrinsic ovarian failure almost invariably excrete *increased* amounts of gonadotropin in the urine Low urinary assays are usually the rule when pituitary secretory activity is diminished Infrequently inconsistent and unexpected results are obtained in urinary gonadotropin determinations This is probably largely due to unavoidable technical imperfections in the tests employed Several different bioassay methods are used in various laboratories, all based on the ability of hormone-containing urinary extracts to induce morphologic changes in the gonads or secondary changes in the accessory genital organs of intact immature animals Procedures differ in details of hormone concentration and extraction test animals dose levels and physiologic end points There is no or little uniformity in the terms in which units are expressed The mere fact that so many methodologic modifications exist attests to the inadequacies of this type of biologic assay Nevertheless despite occasional discordant results urinary gonadotropin assays are usually very valuable in differential diagnosis It must be emphasized however that information derived from this source should not unseat a clinical impression gained by careful evaluation of the patient s history and the results of physical examination It is usually possible to distinguish between primary and secondary ovarian disease on purely clinical grounds Under these circumstances urinary gonadotropin determinations merely serve as corroborative evidence along with other auxiliary laboratory procedures

The great majority of patients with estrogen deficiency fall within the climacteric and castration groups and in women suffering from debilitating systemic disease In the latter class of patient the clinical features of hypogonadism are apt to be obscured by the serious manifestations of the underlying disease While all women with deficient or absent secretion of estrogenic hormone are sterile and amenorrheic they may exhibit varying degrees of disturbance in the developmental state of their secondary sexual characteristics and accessory genital organs The extent to which these are altered depends largely if not entirely on the age of the patient when the failure originated The most advanced changes are found in those women whose estrogen deficiency began before the normal age at which puberty would have been completed

Prepuberal Estrogen Deficiency —Strictly speaking estrogenic hormonal insufficiency is physiologic before the onset of puberty It is only after the subject attains chronologic maturity that the effects of prepuberal deprivation of estrogenic hormone become apparent The genitalia of childhood size persist into adult life with preservation of the infantile cervico uterine ratio The latter characterizes a uterus in which the measurement of the cervix is longer than that of the corpus Under normal circumstances the enlargement of the uterus which occur at puberty is accompanied by an absolute decrease in the length of the cervix A diagnosis of infantile uterus is not tenable in the absence of an infantile type of

therapy is useless It is to be emphasized that therapeutic responses short of pregnancy can be determined accurately only by endometrial biopsy If a progestational endometrium is secured but pregnancy does not follow or if normal ovarian function is not maintained it may be advisable to repeat the series of injections once a year

Estrogenic Failure —In this category are found those instances of female hypogonadism in which all components of ovarian function are deficient Endocrine manifestations are apt to be conspicuous their extent depending upon the degree of hormonal insufficiency If the ovaries are present, the Graafian follicles fail to undergo development or maturation and no corpora lutea are formed The net result of decreased or absent secretion of estrogenic hormone is sterility amenorrhea and a regression or failure of appearance of the secondary sexual characteristics The accessory genitalia likewise may show involution or non-development

Estrogen deficiency may be due to a large number of causes These may originate in the ovaries themselves or the ovarian hypofunction may be secondary to deficient gonadotropic secretory activity of the adenohypophysis The latter may be due to disease in or near the anterior lobe of the pituitary In addition a number of acute and chronic systemic diseases of a debilitating nature may interfere indirectly with ovarian function by reducing the secretory activity of the pituitary The effects of excessive androgen administration are also mediated in this manner The principal causes of estrogen deficiency may be tabulated as follows

1 Primary conditions of the ovaries
 a Climacteric (physiologic or premature)
 b Castration (surgical irradiation or traumatic)
 c Local pelvic disease (bilateral inflammatory cystic degenerative or neoplastic disease)
 d Agenesis
2 Conditions secondary to pituitary disturbances
 a Panhypopituitarism (Simmond disease) craniopharyngioma chromophobe adenoma Frohlich s disease inflammations trauma vascular lesions idiopathic atrophy)
 b Relative hypopituitarism (isolated lack of gonadotropic secretion Laurence Moon Biedl syndrome Sheehan s syndrome)
 c Indirect effects of chronic malnutrition diabetes mellitus renal adrenocortical and thyroid disease Administration of excessive amounts of androgen Masculinizing ovarian tumors

A classification of estrogen deficiency on the basis of whether it is due to intrinsic disease of the ovaries or to defective stimulation by the pituitary is of considerable practical importance from a prognostic and therapeutic point of view In primary ovarian disease which is severe enough to cause manifestations of estrogen insufficiency the ovaries usually cannot be restored to function The hormonal deficit can be overcome only by substitution therapy with estrogenic substances On the other hand when ovarian hypofunction is due to defective adenohypophyseal gonadotropic stimulation the outlook for salvage of ovarian function is hopeful In such cases the ovaries are not diseased but merely regress to an involuted state If this has not lasted too long it is possible in some cases to cause the ovaries to function normally either by removing the cause of the pituitary defect

allergic reactions involved in gonadotropin therapy. For these reasons estrogenic therapy is the procedure of choice in most cases of prepuberal estrogen insufficiency.

Estrogen therapy is indicated primarily for the correction of genital hypoplasia and the production of breast development. Wherever possible it should be instituted *prior to the completion of puberty in order to prevent abnormal skeletal development.* It is not always possible to detect evidences of estrogen deficiency early enough to accomplish this purpose. However, teen age girls who appear to show retarded adolescence should be promptly investigated with this in mind.

The Problem of Delayed Adolescence.—*There are marked individual* variations in the time of onset of puberty and the rapidity with which it develops. The development of secondary sexual characteristics is the first sign of beginning ovarian function. According to Fluhman[19] the earliest evidence begins at about the age of eight years when breast development and urinary estrogens first appear. The *menarche is the most striking* manifestation of puberty and usually appears at about thirteen or fourteen years. However, the range of normal is wide and the initiation of menstrual bleeding may occur between the ages of nine and sixteen years. Uterine bleeding before the age of nine years is to be regarded as evidence of precocious puberty or pseudopuberty. *A delay of bleeding beyond sixteen* years of age signifies retarded adolescence. During the era of adolescence pubic and axillary hair make their appearance and a spurt in general body growth occurs. The vagina and uterus enlarge and the proportions of the latter change toward the adult type in which the length of the cervix *recedes in proportion to that of the corpus.* The *physiologic changes* do not occur in any particular order or pattern so that the child as a whole must be considered when the problem of delayed puberty arises.

Delayed puberty should be suspected in a girl of fifteen or sixteen years of age who has not yet menstruated and who shows slight or absent breast *development. The suspicion is strengthened by absent or sparse pubic* and axillary hair and an absence of typical feminine fat distribution over the hips, shoulders and thorax. If abnormal skeletal development already exists adolescence may be regarded as definitely retarded. Disproportionately long extremities in comparison with the length of the torso, as indicated by an arm span in *excess of the height, is a definitive indication of* estrogen deficiency. Similarly, excessive shortness of stature not explained on a constitutional or familial basis, leads to a strong suspicion of a pathological hormonal deficiency.

In the absence of confirmatory skeletal changes and if there are some evidences of breast and hair development, it is *advisable to observe the* patient until she attains the age of seventeen years in the hope that menstruation and sexual maturity will be attained spontaneously. If, on the other hand, there is definite evidence of pathological estrogen deficiency at any earlier age as evidenced by bony abnormalities and a complete absence of breast, genital and hair development, therapy should be instituted at once.

Laboratory *procedures are often of questionable* value in the diagnosis of border line cases of delayed adolescence. Since urinary gonadotropins

cervico uterine ratio Amenorrhea and sterility of course, are invariably present

The breasts fail to develop as a result of poor or absent mammary stimulation by estrogens Pubic and axillary hair growth is sparse while the hair development on the body and head is normal A generalized deposition of fat frequently occurs Striking developmental changes in the skeleton may occur The pelvis fails to enlarge Abnormalities in the height of the individual and the length of the extremities are common The patient may grow excessively tall because of failure of epiphyseal union Secondary centers of ossification appear in the epiphyses of the long bones but their bony union with the shafts is delayed because of insufficient estrogen secretion

Retarded bone age is readily recognized by roentgen examination of the epiphyseal regions The chronologic age at which epiphyseal closure occurs varies for different bones For example closure of the humerus radius and ulna normally occurs at puberty The epiphyses of the iliac crests do not normally unite until about the age of thirty years Delayed bone age is recognized by the roentgen demonstration usually at the elbows and wrists of epiphyseal non union at a time when closure normally occurs

The non united epiphyseal junctions permit a slow continuous growth of the diaphyses over a longer period of time than would normally be the case if closure occurred at the proper physiologic time i e puberty This results in excessive linear growth of the long bones which produces two types of skeletal abnormality The first is increased total height and the second is a disproportionate length of the extremities in comparison with the torso so that the arm span exceeds the height in measurement This type of skeletal development is reminiscent of that which occurs in prepuberal androgen deficiency in males and is accordingly referred to as *ovarian eunuchoidism*

Not all subjects with prepuberal estrogen deficiency grow tall Some attain a normal height while others retain a short stature When the latter is marked the condition of dwarfism exists Ovarian insufficiency associated with a short stature is characteristic of ovarian agenesis This is a congenital abnormality which is accompanied by a somatic growth defect also presumably congenital in origin The presence of dwarfism (a height usually less than 4 feet) generally signifies that ovarian insufficiency as well as the growth defect are due to a common pituitary disorder

Therapy for patients with prepuberal estrogen deficiency theoretically depends primarily upon whether the ovarian insufficiency is primary or secondary In the former event replacement therapy with estrogenic substances is indicated In the case of a primary defect in pituitary stimulation the condition has usually existed too long to permit the involuted ovaries to respond to stimulation Wherever possible the cause of pituitary suppression should be removed and the ovaries be given an opportunity for spontaneous resumption of function Failing this a preliminary trial with gonadotropin therapy may be of academic interest in so far as ovarian responsiveness may be thus demonstrated However it rarely succeeds in producing ovulation in these patients which would be the only worthwhile reason for subjecting the patient to the inconvenience expense and possible

Hypoestrogenic Osteoporosis — A further osseous effect of estrogen deprivation is the ultimate development of osteoporosis. This has been carefully studied in postmenopausal women by Albright and his colleagues [14,15,16]. These workers believe that a lack of estrogen results in decreased osteoblastic activity which in turn causes a defective matrix. The latter is the protein-containing substrate in which calcium and phosphorus are deposited to produce normal calcification and ossification. In the absence of adequate or mature bony matrix, calcification is defective resulting in the poorly mineralized condition known as osteoporosis. According to this concept osteoporosis is therefore due to a defect in matrix formation and not to a disorder of calcium metabolism. The physiologic effects of the estrogenic hormone on the osseous system are discussed in the previous chapter, p. 579.

Postmenopausal osteoporosis is almost exclusively confined to the vertebral and pelvic bones. It occurs some years after induced or spontaneous menopause and accounts for the great majority of cases of osteoporosis in women between the ages of forty and sixty years. The characteristic localization of osteoporosis to the vertebrae is readily recognized by roentgen examination. In addition to marked demineralization of the vertebrae, alterations in their configuration may occur as a result of decreased resistance to pressure. Wedging of the anterior segments of the vertebral bodies in the dorsal region may lead to a rounding of the back. Vertebral collapse and compression fractures are occasionally noted in the more advanced cases. The subject of postmenopausal osteoporosis has been reviewed recently at length by Snapper[17] whose book also presents excellent reproductions of characteristic roentgen findings.

Vertebral osteoporosis also occurs in young women whose estrogen deficiency appeared prior to the completion of puberty. Patients with ovarian agenesis often manifest this condition as young adults. In addition, Albright and Reifenstein[16] point out changes along the borders of the vertebral bodies which they ascribe to irregular ossification of the epiphysial plates. Delay in the fusion of the vertebral epiphyses, which normally occurs at about the age of twenty five years, produces spotty calcification along the superior and inferior borders of the vertebral bodies. Erosions and irregularities of these margins are also frequently noted. The roentgen appearance of these changes is usually termed "epiphysitis" or "osteochondritis" by roentgenologists, although there is certainly no inflammatory element present.[16] These x ray findings are identical with those found in Scheuermann's disease (juvenile dorsal kyphosis), a condition of unknown etiology. It is therefore quite possible that an unrecognized estrogen deficiency may account for this disease in some patients.

In contradistinction to the non-occurrence of postmenopausal osteoporosis outside the spine and pelvis, Wilkins[7] reports a moderate degree of osteoporosis in the carpus, tarsus and ends of the long bones in patients with ovarian agenesis.

Hypoestrogenic vertebral osteoporosis is symptomatically benefited by the administration of gonadal steroid hormones. Although the natural therapeutic inclination would be in the direction of replacement therapy with estrogens, the use of androgens appears to be more effective. This is due to the fact that androgens exert a more marked effect than estrogens

make their appearance at the time of puberty, their complete absence in a sixteen-year-old girl suggests hypogonadism of pituitary origin. On the other hand, an excessive urinary excretion of gonadotropins denotes primary ovarian failure. An increased gonadotropin titer may be found as early as twelve or thirteen years of age in these conditions. Determinations of urinary estrogens, androgens and neutral 17-ketosteroids are of little diagnostic assistance since these levels are usually subnormal before puberty is completed. Roentgen examination of the elbows and wrists may reveal retardation of bone age as an indication of hormonal insufficiency. The possibility of an underlying hypothyroidism is readily excluded by the clinical appearance, basal metabolic rate and blood cholesterol level. Other evidence of associated endocrine gland disorders must be sought for in the evaluation of any problem of delayed gonadal function. These include adrenocortical and pituitary disease, the diagnosis of which is discussed elsewhere.

Other causes of delayed menarche and adolescence include constitutional, hereditary and environmental factors. Malnutrition and systemic diseases such as renal disorders, diabetes mellitus and tuberculosis may be etiologic factors.

Therapy of delayed adolescence is begun when it is certain that maturation will not occur spontaneously or when definite evidence of pathological estrogen deficiency exists. In any event it should not be delayed beyond the age of seventeen years lest irremediable skeletal changes supervene. Recognizable causative factors should be removed or treated. When adolescence is delayed because of a primary disturbance of the ovary, treatment should be substitutional with estrogens. By this means normal genital, breast and hair development can be induced. Closure of the epiphyses will be favored, thus preventing excessive tallness. On the other hand, this effect is not to be desired in subjects who are very short. However, there is no convincing evidence to indicate that estrogen administration interferes with *normal* growth.

Estrogen therapy should be administered cyclically and continued for three or four months. Oral preparations are preferable because they are inexpensive and conveniently taken. Diethylstilbestrol 0.5 mg., naturally occurring estrone sulphate 0.625 mg. or ethinyl estradiol 0.05 mg. are taken daily (or preferably at night in the event that they produce nausea) for three weeks. This is followed by rest from treatment for one week, after which therapy is resumed in the same interrupted manner for another 2 or 3 cycles. This amount of therapy usually results in some enlargement of the breasts, pigmentation of the areolae and development of the genitalia. Pubic and axillary hair growth may be stimulated. A rest period of three to six months is then allowed to see whether the induced development is maintained spontaneously. This occasionally occurs and even periodic uterine bleeding may follow.

Should regression of development follow cessation of therapy, estrogenic treatment on a long term basis must be provided if the effects of permanent estrogenic insufficiency are to be avoided. This is best accomplished by continuing cyclic oral administration.

therapy are two in number. First, are those patients whose climacteric symptoms do not respond to conventional treatment with sedation, reassurance and improved hygienic conditions. Second, are patients with vertebral osteoporosis. Since these conditions as a rule develop only in patients with *primary ovarian failure, hormone therapy directed against* estrogen insufficiency is rarely indicated in cases of secondary failure. Patients whose hormonal insufficiency is due to intrinsic ovarian disease and who have genuine indications for replacement therapy should be given estrogens. A program of therapy is outlined in the discussions of osteoporosis and the climacteric. The general principles and technics of estrogen therapy are considered in the next section.

Principles and Technic of Estrogen Administration.—The great abundance of estrogenic preparations available for clinical use usually presents a confusing problem to the prescribing physician. These products are of 4 different varieties. Some are derived from the urine of pregnant mares or women and contain mixtures of estrogen conjugates. Others are obtained in crystalline form as estradiol, estrone and estriol from natural sources. A few are natural estrogens which have been modified by chemical procedures, such as ethinyl estradiol. Finally, there is the group of synthetic non-steroidal stilbene derivatives headed by diethylstilbestrol.

Estrogens may be administered parenterally, orally or locally by vaginal instillation or inunction. They may also be implanted as pellets subcutaneously. As a rule, the selection of the route of administration in a particular case is governed by the existing therapeutic indications and extenuating circumstances.

Among the estrogens most widely employed for parenteral use are the pure crystalline forms. These include estrone, estradiol and its slow-acting esters, estradiol benzoate and dipropionate. The vehicles are usually oils to provide for further slowing of absorption. Aqueous suspensions of relatively insoluble microcrystals of pure estrogen (estrone and estradiol) have recently been introduced in an effort to prolong biologic action.[46] The object is to provide a depot from which the microcrystals, acting as micropellets, are slowly and continuously absorbed into the blood stream. The therapeutic efficacy of this method has not yet been definitely established. In addition, certain naturally-occurring non-crystalline estrogens are available for injection use. These owe their biologic activity principally to their estrone content. Finally, the synthetic estrogen, diethylstilbestrol, is also prepared for parenteral use.

Available oral preparations include crystalline estradiol and estriol. More popular are the non-crystalline natural estrogens in the form of estrone sulphate and estriol glucuronide. The stilbene non-steroidal derivative diethylstilbestrol and the recently introduced ethinyl estradiol round out the list of orally effective products. In general, most estrogens are considerably less effective by the oral route than when administered parenterally. This is due to the destructive effect of intestinal action and the reduction in biologic activity which occurs during hepatic inactivation. In the case *of some of the crystalline and conjugated estrogens the loss can be compen*sated for by the use of proportionately larger (10 to 20 times) oral doses. This is also true of diethylstilbestrol, which, however, is not as greatly in

on protein metabolism and electrolyte retention According to Snapper[17] the administration of the male hormone results in an increased deposition of protein matrix permitting subsequent recalcification of the bone He finds that a favorable symptomatic effect can be obtained by thrice weekly intramuscular injections of 25 mg of testosterone propionate By keeping the monthly dosage below 300 mg, undesirable masculinizing effects can usually be avoided The occasional development of hoarseness and slight hirsutism can often be offset by the simultaneous biweekly administration of estrogens When estrogens are administered concurrently, as much as 500 mg of testosterone propionate can be injected in one course of treatment without causing masculinization[78]

Reifenstein and Albright[18] favor the use of 25 mg of testosterone propionate given intramuscularly once a week or 10 to 20 mg of methyltestosterone daily by mouth for the first six to twelve weeks At the same time estrogenic therapy is instituted Although parenteral administration is satisfactory it is generally more convenient and less expensive to employ the oral route Diethylstilbestrol 0 5 mg naturally occurring estrone sulphate 0 625 mg or ethinyl estradiol 0 05 mg are satisfactory for this purpose The daily administration of estrogens should be interrupted periodically every month for one week, in order to avoid excessive estrogenic stimulation of the uterus

Although the back pain often disappears and a generally favorable response frequently follows gonadal hormone therapy, recalcification of bone is rarely demonstrable in the roentgenogram[17]

Hypogonadal vertebral osteoporosis has its counterpart in the male where however it appears to be extremely uncommon This subject is discussed in the chapter dealing with diseases of the testis p 464

Postpuberal Estrogen Deficiency —When a postadolescent woman is bereft of her ovarian estrogenic hormone the effects are not nearly as marked as they are when this occurs prepuberally Except for sterility and amenorrhea or scanty menses recognizable objective changes in the genitalia and mammae may not appear for a long time Such an individual may be indistinguishable from a woman with normally functioning ovaries Eventually however the uterus becomes small and fibrous and the endometrium atrophic The volume of the vagina is ultimately reduced and its mucosa undergoes atrophy Regressive changes slowly occur in the breasts A slight regression in the amount of pubic hair may also occur Vertebral osteoporosis is an occasional finding The slow rate of mammary decline and change in body hair observed in the postpuberal ovariectomized woman may be due in part to continued estrogen production by the adrenal cortex[13]

A train of distressing subjective symptoms may appear in the wake of postpuberal estrogen deficiency These consist of numerous vasomotor and psychogenic complaints which appear most characteristically in menopausal women For this reason a discussion of these phenomena is reserved for the section dealing with the climacteric

Therapy in patients who develop estrogen deficiency after the completion of puberty is not always necessary In fact apart from sterility and amenorrhea the endocrine disturbances are often so mild that they require no specific hormonal therapy at all The principal reasons for endocrine

therapy are two in number First are those patients whose climacteric symptoms do not respond to conventional treatment with sedation reassurance and improved hygienic conditions Second are patients with vertebral osteoporosis Since these conditions, as a rule develop only in patients with primary ovarian failure hormone therapy directed against estrogen insufficiency is rarely indicated in cases of secondary failure Patients whose hormonal insufficiency is due to intrinsic ovarian disease and who have genuine indications for replacement therapy should be given estrogens A program of therapy is outlined in the discussions of osteoporosis and the climacteric The general principles and technics of estrogen therapy are considered in the next section

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activated when given orally. Parenteral administration is only 3 to 5 times as effective as the oral method. Ethinyl estradiol, on the contrary, is as active orally as it is by injection and therefore requires but very small doses.

Vaginal suppositories consisting of estrogens are employed where local action on the vaginal structures is desired in cases of gonorrheal vaginitis in children and senile vaginitis.[4] Undesirable endometrial and systemic effects may thus be avoided. Preparations containing crystalline estradiol and estrone and non-crystalline estrogen conjugates are available.

Estrogens are also available for use by inunction. They are used in this form principally for the purpose of stimulating poorly developed breasts. Some stimulation occurs in this manner, but the amount due to the local action of the hormone and that derived from the non-specific effect of massage is difficult to evaluate. Attention is called to the fact that percutaneous absorption of estrogens occurs so that some general stimulation may result.[23] For this reason the use of "estrogenic" cosmetic creams is to be deprecated. Ointments for clinical use contain crystalline estradiol and non-crystalline conjugated estrogens.

For long-continued substitution therapy the subcutaneous implantation of estrogens in the form of pellets has been recommended as an effective procedure.[9, 14, 143] This method insures slow continuous absorption of the estrogen over a long period. Its use should always be preceded by a course of injections in order to determine the required weekly dose. The effect of pellets may last from two to six months. Occasionally the implanted dose proves too large, in which event removal of the pellets becomes necessary. Although pellet implantation is ideal whenever prolonged effects are desired, its application to the administration of estrogens raises certain objections. In general, estrogen therapy should be interrupted rather than continuous. This simulates normal physiologic conditions and avoids excessive uterine stimulation and bleeding.

A good deal of uncertainty centers about the selection of an estrogen for clinical use in a given case. In the first place the decision must be made as to whether parenteral or oral administration is preferable. The administration of a hormone by injection has certain positive advantages. The delivery of a known effective dose into the organism is assured. Moreover, the patient remains under the observation of the physician so that her progress can be more accurately followed. If oily solutions of estradiol esters are employed, injections may only be required every five to seven days. However, several factors detract from these advantages. The unpleasantness of injections and the inconvenience and expense incurred by repeated visits to the physician may pose important obstacles to the patient. In some cases this may interfere with her receiving necessary treatment.

The orally effective estrogens eliminate the disadvantages of parenteral administration. They are inexpensive and their daily administration is more effective in securing constant levels of hormones in the body. This more closely simulates physiologic conditions than do periodic injections. The more slowly acting esters of estradiol (benzoate, propionate, dipropionate) provide for slow absorption after injection. However, there is

no proof that they yield steadier blood levels than those obtained by the daily administration of oral estrogens. On the other hand, methods of oral therapy are not devoid of disadvantages. Some orally potent estrogens induce nausea, vomiting, dizziness and headache in certain patients. It is a matter of interest that these effects are rarely if ever observed in pregnant or parturient patients. Another objection to oral therapy is that it leads to self medication on the part of the patient. Not all individuals can be relied upon to follow directions implicitly. Moreover, it is not uncommon for certain patients to continue to refill the original prescription without the physician's knowledge or long after the original therapeutic indication ceased to exist. Undesirable and at times frightening uterine bleeding may be caused in this manner. Wherever possible, however, oral therapy with estrogens is preferred to parenteral administration.

The question of units and equivalent dosages of the various estrogenic substances has been rendered very difficult to evaluate for several reasons. The large variety of commercial preparations and the frequently unsubstantiated claims of their manufacturers with regard to comparative potency have clouded the situation. The lack of a satisfactory nomenclature and concise therapeutic standards are additional factors.[3]

Existing standards for estrogens do not apply to the entire spectrum of available products. Crystalline estrogens are standardized in accordance with a reference standard for estrone adopted by the Health Organization of the League of Nations. One international unit of estrone equals 0.0001 mg. (or 0.1 gamma). The employment of the international standard for estrone has made possible a basis for comparison of the results of the various bioassay methods in use in different laboratories. Each investigator or manufacturer is now able to compare the results of his own assays with those of a known amount of estrone. He can then express his results in terms of the internationally accepted estrone equivalent.

Since the international unit applies only to estrone, it cannot be used to state accurately the potency or content of mixtures of estrogens. The potency of these latter preparations can only be expressed as rat units (which measure total estrogenic potency) or as international units of estrone. The latter, of course, does not express the full estrogenic content of the mixture. Just as the rat unit may be used to assay mixtures of estrogens, it may also be employed in assays of pure estrone. In this case 1 rat unit of estrone equals 10 international units or 0.001 mg. However, the rat and international units for pure estrone are not equivalent to those of other estrogens.

There is another international unit for the benzoylated estrogens which is called the international benzoate unit. The I.B.U. for estradiol benzoate equals 0.0001 mg. It cannot be compared to the international estrone unit because of the more prolonged action of estradiol benzoate as compared with that of pure estrone.

K. W. Thompson[4] has recently reviewed the problem of estrogen units. He points out an additional source of confusion in the usage of rat units when applied to short- and long-acting estrogens. For example, estradiol benzoate and dipropionate are highly effective over a long period of time. Yet assays reveal fewer rat units per milligram than in the case of the

short acting alpha-estradiol. Two reasons account for this difference. First is the presence of the ester in the molecule. Second, and more important, is the fact that rat unit potency is determined on a stated day after injection into the animal. This corresponds to the day of greatest effect of estrone or estradiol. If the test day were delayed, it would be found that the long acting preparations would still be showing an effect whereas the estrone or estradiol would have ceased action.

In an effort to establish a working arrangement Thompson has calculated a list of equivalents. This is offered with an understanding of the limitations of bioassay methods, but nevertheless provides an approximate basis for comparing estrogenic potencies. The first group shows the comparative potency per milligram of various estrogens. The second group compares different estrogens in terms of equivalent potency. It is to be emphasized that the comparative potencies of estrogens as determined in the experimental animal do not necessarily apply to humans. Assays employing human subjects would be more accurate in this respect. Although several efforts in this direction have been made[3, 6, 27, 28, 44, 50] there is room for much further study. Thompson's list of estrogen equivalents is as follows:

	Rat Unit	*International Unit*
1 mg ethinyl estradiol (oral and parenteral)	12 000–14 000	120 000–140 000
1 mg estradiol (parenteral)	12 000	120 000
1 mg estradiol benzoate (parenteral)	6 000	
1 mg estrone (parenteral)	1 000	10 000
1 mg estriol (parenteral)	150	1 500
1 mg diethylstilbestrol (parenteral)	5 000	50 000

2 000 R U estradiol benzoate (parenteral)	10 000 I U estrone
5 mg diethylstilbestrol (oral)	5 mg estrone (parenteral)
52 to 63 mg estradiol (oral)	0 65 mg ethinyl estradiol (oral)
1 mg diethylstilbestrol (parenteral)	1 mg estradiol benzoate (parenteral)
1 mg diethylstilbestrol (oral)	1 mg conjugated estrogens (oral)

This figure has dubious value because of the long action.

When estrogens are employed for purposes of substitution therapy they should be administered with a view to reduplicating the hormonal state which exists under physiologic conditions. Since the ovarian follicles secrete estrogen in cyclic fashion the therapeutic administration of estrogenic hormone should also be cyclic. The simplest plan to follow is to supply the hormone for three weeks out of every four. This may or may not result in withdrawal bleeding during the week when no therapy is given. Small enough doses usually prevent it. Larger doses will induce withdrawal bleeding which may at times be desirable. In any event, in addition to being sounder physiologically, interrupted treatment prevents undue uterine stimulation. Under conditions of prolonged and excessive hormone administration the latter may produce uterine hemorrhage.

The question of estrogen carcinogenicity in the human female has not yet been definitely settled. Certain isolated case reports in the literature suggest that the prolonged administration of estrogens may have been re-

sponsible for the development of female mammary cancer [9-31] There is no proof that estrogens are a direct cause of breast malignancies although it is well known that their administration can result in acute exacerbation of breast and genital carcinoma which existed previously In general it is advisable not to administer estrogens in large doses or for a prolonged period of time when there is a family history of cancer without initial and repeated examination of the uterus and both breasts This is also true of patients with chronic mastitis cancer, or any other form of breast neoplasm either before or after surgical or radiation treatment [30 32]

Because of the ability of estrogens to favor sodium and water retention, estrogens should be administered cautiously if at all to elderly patients or others with poor cardiac reserve Peripheral and pulmonary edema may follow the injudicious use of estrogens in these patients

Principles and Technic of Gonadotropin Administration —In patients whose ovaries have been deprived of adequate pituitary gonadotropic stimulation it is often desirable to attempt to reproduce the physiologic state by the exogenous administration of suitable extracts The word "attempt" is employed advisedly because of the frequent inefficiency of this type of therapy The first prerequisite is an ovary which is capable of responsiveness This will not be the case if it has been in an involuted state for too long a time The second requirement is a potent gonadotropic extract capable of supplying one or both of the necessary tropic factors In actual practice this objective is often not realized although chances for success do not appear to be as minimal as stated by Davis [40]

Gonadotropin therapy is indicated only when ovarian failure is due to a lack of adequate adenohypophyseal gonadotropic factors In these instances urinary gonadotropin assays usually reveal low or absent titers Therapy is invariably futile if the condition has been of long duration or if underlying disorders of the thyroid or adrenal cortex are not removed The presence of debilitating systemic disease will also militate against therapeutic success

The most accurate means of evaluating therapeutic effectiveness would be by histologic examination of the ovaries before and after treatment In this way follicle growth ovulation and corpus luteum formation could be readily identified This of course is not feasible and accounts for the fact that the anatomic effects of gonadotropin therapy in the female are not as well known as they are in the male where testicular biopsy is a relatively simple procedure Lacking morphologic criteria in the ovaries themselves reliance for the evaluation of therapeutic effects must be placed on indirect evidence of stimulated ovarian function For this purpose basal body temperature records vaginal smears urinary pregnanediol excretion and endometrial biopsies are available

Three groups of gonadotropins derived from different sources are available for clinical use Although these preparations are capable of producing normal ovarian function in certain immature and hypophysectomized laboratory animals clinical results in the human are often indifferent or disappointing

Adenohypophyseal Gonadotropins —Theroretically these would be most ideal but unfortunately current methods of extraction and purification

have failed to produce highly potent material free from undesirable reactions. The use of human pituitary glands is obviously impracticable and animal sources are utilized instead. This involves the introduction of a foreign protein into the human organism and invites antibody formation.

Leathem[33] has recently reported the results of extensive observations on antihormone production using the various available gonadotropins. Continuous therapy with commercial extracts of FSH derived from sheep and horse pituitary commonly leads to antihormone formation. Maddock[34] studied antihormone production in response to pituitary gonadotropins in the male. He demonstrated that antihormones not only inhibit the action of injected FSH but also neutralized the effect of the host's own pituitary gonadotropins. That this is accomplished by the formation of an inactive hormone-antihormone combination rather than by destruction is indicated by the continuous urinary excretion of endogenous gonadotropins at a time when maximal amounts of antihormone are present in the plasma. Apparently the kidney effects a separation of the hormone-antihormone combination permitting the gonadotropin to be excreted while the antigonadotropin is retained. Further experiments indicate that, at least in the male, neutralization of endogenous pituitary gonadotropins by antihormones results in further depression of gonadal function.[35] This undesirable effect can be prevented by interrupting treatment by a rest period after five to six weeks.

In their present state of impurity, low potency and ability to induce reactions, pituitary gonadotropins are not widely used at this time.

Equine Gonadotropin. — This gonadotropin is secreted by the placenta of the pregnant mare and is unique in that it is not excreted in the mare urine. However, it is abundantly present in pregnant mare serum and is therefore called PMS. Its properties are dissimilar from either pituitary or chorionic gonadotropin, although its biologic actions resemble a combination of both FSH and LH, predominantly the former. Follicle growth, ovulation and corpus luteum formation can be readily induced in many laboratory animals with this hormone. Results in the human are promising where follicle stimulation is sought. Hamblen[71] has obtained successful results in cases of anovulatory sterility with a ten day course of PMS followed by the use of chorionic gonadotropin for ten days. After preliminary skin testing, 400 international units of PMS are injected intramuscularly each day for ten days starting on the fifth day of the cycle. This is followed by another ten days of treatment with chorionic gonadotropin which is given for its luteinizing and luteotropic effect. Daily intramuscular injections of 500 international units each are administered from the fifteenth to the twenty-fourth day. Injections are stopped if bleeding occurs during the therapy. The further schedule of treatment is discussed in the section dealing with anovulatory failure, p. 627.

It is to be noted that the gonadotropin principle contained in the serum of pregnant mares (PMS) is also capable of producing antihormone. However, this tendency is much reduced when purified low nitrogen preparations are employed.[33] The development of antihormones inhibits the action of the injected hormone on the target organ and so reduces therapeutic effectiveness. For this reason the mode of its administration is of utmost

importance if successful results are to be obtained Leathem[33] points out that antihormones are induced more readily by daily than by weekly injections However, the risk of developing significant amounts of antihormone with daily injections over a ten day period does not appear to be great When the cycles of gonadotropin therapy are to be repeated Rakoff[34] recommends alternation of gonadotropin preparations as a further measure in the avoidance of antihormonal responses

Allergic skin and constitutional reactions are quite uncommon and are not to be confused with the question of antihormone response Only 1 case of allergy developed during PMS therapy in Leathem's[33] experience He calls attention however to a near fatal reaction[37] We have observed a single instance of severe local tissue reaction about the site of injection This occurred after the third daily injection and required four days to subside Previous intradermal test was negative After an interval of one month desensitization was begun starting with 1/50 of the original dose By cautiously and progressively increasing the doses it was possible to approximate the original dose without producing a disturbing reaction This case is cited to demonstrate the possibility of effective desensitization in selected instances This may be desirable in so far as allergic reactions do not interfere with clinical results There appears to be no correlation between reactions of hypersensitiveness and the presence of antihormones[38]

Chorionic Gonadotropin —This gonadotropin is utilized principally for its luteinizing and luteotropic effects These have been amply demonstrated in the laboratory animal and there is convincing evidence of a similar effect on the human ovary[5 7 33 39 41] By itself it has no influence on follicle development As stated above its use in conjunction with follicle stimulating preparations such as PMS may be effective in promoting final follicle maturation and ovulation In large enough doses it is capable of enhancing and prolonging the effect of a normal human corpus luteum This results in the production of pseudopregnancy a state characterized by delayed menstruation a positive pregnancy test (Aschheim Zondek Friedman) in the urine prolonged urinary excretion of pregnanediol and endometrial biopsies showing decidual changes[38 39]

Commercially available chorionic gonadotropin is prepared from human pregnancy urine or placenta For this reason antihormone formation is not to be anticipated and in fact Leathem[4] was unable to demonstrate it after extended use of the hormone

Chorionic gonadotropin is ordinarily administered as intramuscular injections of 500 international units daily or 1000 international units every other day Its use is generally timed for what may be expected to be the luteal phase of the ovarian cycle It is therefore administered during the ten days or two weeks prior to expected menstrual bleeding It may be used alone as in the treatment of pure corpus luteum deficiency or after a preliminary course of follicle stimulating (FSH) therapy as in the therapy of anovulatory sterility or amenorrhea Commercially available solutions employ an aqueous vehicle Recent experiments designed to test the possible prolonging effect of an oily vehicle showed that there is no advantage in using such a medium[43]

The Climacteric.—Like the beginning, the end of woman's reproductive life is characterized by a gradual transition. The word "climacterium," derived from the Greek, means "rung of a ladder," and best describes the idea of a transitional step in the course of physiologic aging. Since it covers a phase lasting an average of one to three years, climacteric is a more meaningful term than menopause, which simply refers to the cessation of menstruation. The disappearance of menstrual bleeding is only one part of a general retrogressive process, and, strictly speaking, does not convey the full significance of the climacteric.

The total duration of active ovarian function usually ranges between twenty-five and thirty-five years, with an average of thirty-three years.[45] There is also a wide variation in the age at which menstrual function ceases. Race, heredity, climate and general health are believed to be factors in causing individual variations. In the average case menstrual bleeding disappears between the ages of forty-five and fifty years. Some women still menstruate in their fifties. Menstruation beyond the age of sixty years is extremely dubious and, when encountered, calls for a thorough search for organic disease. For example, estrogen producing granulosa cell tumors may cause uterine bleeding which simulates the menstrual flow. The spontaneous disappearance of menstruation below forty years of age is regarded as precocious or premature.

As a general rule, the final disappearance of menstruation is preceded by some variety of menstrual irregularity. In a minority of women periodicity is maintained until it is terminated abruptly. The majority lose their menses gradually, often with increasing intervals of amenorrhea punctuated by episodes of sparse bleeding. Occasionally, the irregular uterine flow may be profuse and may occur at less than monthly intervals. While this may be normal for some women during the climacteric, its persistence for more than a few months calls for gynecologic investigation into the possibility of an organic disease, especially malignancy.

In addition to the loss of menstrual function, ovulation also disappears some time during the climacteric. According to Novak,[48] the two functions do not vanish simultaneously. Although ovulation may persist until the very last flow or rarely for six months to a year later, it often disappears before the menopause is complete. Under these circumstances, the terminal menstrual cycles are anovulatory, a matter of practical importance in the evaluation of infertility problems in women approaching their forties.[48]

The principal endocrine alteration which occurs during the climacteric is the gradual loss of estrogenic function. This accounts not only for the disappearance of menstruation and ovulation but also for regressive changes in the accessory genitalia, breasts and secondary sexual characteristics. Moreover, a train of symptoms and signs referable to the sensory, vasomotor, psychic and general somatic systems are prone to appear. There is no general or characteristic pattern in which these numerous changes occur. For example, it is not uncommon to find vasomotor symptoms such as flashes and sweating at a considerable interval before or after the menses disappear. Furthermore, regressive changes in the genital system may not appear until some years after the menopause. Under these circum-

stances the small amount of estrogen produced by the ovaries (or adrenal cortices) is apparently sufficient to maintain the genitalia for some time. At the same time this quantity of hormone is insufficient to produce menstruation or to prevent disturbances in the circulatory or nervous system.

The effects of the climacteric are the same regardless of whether it occurs prematurely or late in life. They are also the same as those resulting from the removal or destruction of functioning ovaries. They do not occur, of course, in the hysterectomized young woman until she attains an age at which her ovaries undergo spontaneous regression. This may occur somewhat earlier than usual, especially if ovarian circulation is inadvertently compromised during the operation. Manifestations of the climacteric are also lacking in women with prepuberal estrogenic failure for obvious reasons. Never having had the benefit of estrogenic stimulation, these individuals cannot experience the effects of estrogen withdrawal.

The uterus progressively decreases in size as it undergoes fibrous replacement. The endometrium shares in the general process of atrophy. However, attention is called to the fact that marked degrees of endometrial proliferation are occasionally found years after the menopause.[7] Its significance is not clear, although Hamblen suggests that in the absence of recognizable causes for estrogenic stimulation, such endometrial changes may represent unusual sensitivity to the small amounts of estrogen supplied by the involuting ovaries.

The vagina becomes reduced in size and its mucosa is transformed into a thin atrophic layer. The absence of glycogen from its cells results in a loss of the normal acid reaction of the vaginal secretion.

The breasts become flabby and apron-like as the parenchyma undergoes atrophy.

General physical alterations include a tendency to gain weight due, particularly, to a deposition of fat about the hips. Pubic and axillary hair tends to become sparse and the skin may lose its resilience and smooth fine texture.

Subjective symptoms may be completely absent. This has been estimated to be the case in about 15 per cent of climacteric women.[49] More often they are present as a characteristic group of phenomena headed by sweats and sensations of body warmth. Novak[48] draws a technical distinction between hot flushes and hot flashes which serves a useful purpose from a descriptive point of view. Hot flushes refer to the warmth and redness which patients experience over the head, neck and upper thorax. The less frequent sudden surges of heat which may involve the whole body are called hot flashes. A few, many or all of the following manifestations may appear in addition. These are less characteristic than the above mentioned vasomotor symptoms and at times their presence is a coincidence rather than an effect of the climacteric. Frequently encountered are nervousness, fatigability, lassitude, excitability, lightheadedness, vertigo, paresthesias, palpitations and dyspnea. Less often are suboccipital headache radiating into the back of the neck, generalized headache and cold hands and feet. It will be readily appreciated that all of these supplementary symptoms may occur in non-menopausal purely psychogenic or anxiety states. Even

during the climacteric a substantial portion of the total symptomalogic picture may be due to non-endocrine causes

As previously mentioned some women pass through their climacteric without any noticeable distress According to Hamblen[7] who voices the opinion of the majority of observers 70 to 90 per cent of healthy women experience no significant disability

Climacteric Alterations in Hormone Levels —The outstanding endocrine changes involve the secretions of the ovaries and the adenohypophysis Ovarian estrogen and progesterone gradually disappear The reduction in the amount of circulating estrogen removes the normally present estrogenic inhibitory effect on the pituitary This permits excessive pituitary gonadotropic secretory activity As a result increased quantities of gonadotropin (principally FSH) appear in the blood and urine Of all hormonal alterations resulting from the climacteric, the increased urinary excretion of gonadotropins is the most characteristic

Estrogens —Estrogenic hormone continues to be excreted in the urine after the menopause Although very small amounts may be derived from the slowly involuting ovaries for some time most of the postclimacteric urinary estrogen originates from the adrenal cortex Pertinent references in support of this view are cited by Hamblen[7] The quantity of estrogenic material *excreted by the postclimacteric woman is much less than that eliminated* during active reproductive life Early in the climacterium excreted levels approximate those of normal men (about 9 to 12 micrograms as estrone equivalent per twenty four hours) With the advancement of age urinary estrogenic titers fall to mere traces or may disappear entirely

Pregnanediol —The absence of the corpus luteum hormone results in the virtual disappearance of its chief urinary metabolite pregnanediol However minimal traces of urinary pregnanediol can occasionally be demonstrated after ovarian function has ceased[52] This is probably due to adrenocortical elaboration of progesterone or other pregnanediol precursors

Androgens —The urinary excretion of androgenically active material is decreased to less than 10 international units of androsterone equivalent per twenty four hours[53] Between 42 and 56 international units are excreted daily by women during their active sexual lives Decreased urinary excretion of androgens occurs with advancing age in both sexes and probably indicates a diminished function of the gonads as well as the adrenal cortices[54] *Conflicting results have been reported* concerning the effects of ovariectomy in young women on the urinary excretion of androgens[55] Low normal and elevated levels have been observed but subnormal values are most frequently encountered

Neutral 17 Ketosteroids —Dramatic transient increases in the urinary excretion of neutral 17 ketosteroids have been reported from one laboratory[56 57 58] in ovariectomized and *postclimacteric women* These have not been confirmed by others[55 59] who report essentially unchanged excretion levels if one allows for the effect of age The maintenance of neutral 17 ketosteroid excretion in the presence of substantially reduced androgen excretion is not readily explained The differential excretion of adrenocortical metabolites after disappearance of ovarian function is probably

related to variations in secretory response of the different elements of the adrenal cortex.

Urinary Gonadotropins.—As previously stated, the urinary excretion of pituitary gonadotropins is markedly increased. This finding is an almost invariable accompaniment of primary ovarian failure, assuming that the adenohypophysis is capable of reacting normally. Excretion values are 13 to 50 times the normal preclimacteric levels and actual pituitary gland bioassays reveal an FSH content about 10 times normal.[7] There is no evidence to suggest that the greatly increased gonadotropic activity of the pituitary is etiologically related to the production of the climacteric symptoms. This phenomenon is a result and not a cause of ovarian insufficiency and relief of symptoms by substitutional or nonspecific treatment is usually accomplished without affecting the gonadotropin level in the organism. It is to be noted, however, that large enough doses of estrogens (as well as androgens) are capable of abolishing increased urinary gonadotropins. The use of such large doses is rarely required clinically.

Treatment of the Climacteric.—From the point of view of therapy the castrated woman is included along with the climacteric patient. As previously mentioned, there are often no distressing symptoms and no particular treatment is indicated. Many women approach the menopause with unfounded anxiety and apprehension. This psychologic state is often sufficient by itself to produce psychoneurotic manifestations well in advance of the physiologic period of estrogen decline. Their persistence into the epoch of the climacteric often accounts for symptoms which, to the dismay of the patient and physician, do not abate under adequate hormonal therapy. It is, therefore, important that prospective or actual climacteric women be given a simple talk in which several truisms should be emphasized. It may be explained that the loss of reproductive function does not interfere with libido or sexual attractiveness. General somatic deterioration and senility are not the natural accompaniments of the climacteric. Patients should be reassured that adaptation of their body organs to the new hormonal pattern eventually occurs with a complete restitution to a state of well-being.

In the majority of cases, patients with climacteric symptoms respond well to simple psychotherapy and the administration of mild sedatives. These measures should always be employed first before prescribing hormonal substitution therapy.

Estrogen therapy is indicated for a relatively small group of patients whose distress is not relieved by conventional methods of nonspecific treatment. These are the women whose flushes and sweats recur many times during the day and night, often interfering with adequate rest and sleep. Before therapy is started a thorough examination of the pelvic organs and breasts should remove the possibility of organic disease which might be adversely affected by the administration of estrogens.

The principles underlying the selection of a particular estrogen and its route of administration have been discussed in a previous section (page 635). Because of the large number of commercially available estrogenic preparations and the difficulty in evaluating their comparative potencies, it is generally advisable to employ 2 or 3 representative products exclusively



Fig 58 —Vaginal smears illustrating effect of estrogens in ovarian insufficiency The contrasting colors of the immature non cornified vaginal epithelial cells (blue green) and the mature cornified cells (pink) are not apparent in the black and white reproductions The cells can be distinguished nevertheless by their morphologic characteristics In addition to the attainment of cornification the maturing cell under estrogenic influences grows larger and thinner while its nucleus becomes very small The smear becomes cleaner with fewer leucocytes (Shorr Single Differential Stain Medichrome Clay Adams Co Inc Dr Ephraim Shorr New York Hospital—Cornell University Medical Center)

(Legend continued at foot of page 647)

In this manner one gains experience in their use and is in a better position to appraise therapeutic effectiveness. Oral therapy is most widely employed and possesses many advantages over parenteral treatment which is seldom really indicated. The most popular oral preparations are the artificial synthetic estrogen diethylstilbestrol, the water-soluble conjugated estrogens derived from pregnant mares's urine (occurring chiefly as sodium estrone sulphate) and the chemically modified natural estrogen, ethinyl estradiol. Effective doses of these substances vary considerably for different patients. It is advisable in the beginning to use somewhat larger than maintenance doses *in order to secure a rapid effect.* Once palliation is obtained the dose can be lowered to that which maintains relief. Recommended initial doses are

diethylstilbestrol	0.5 mg
sodium estrone sulphate	0.625 mg
ethinyl estradiol	0.05 mg

Estrogen therapy should not be administered continuously. Uninterrupted stimulation is physiologically unsound and may lead to distressing endometrial proliferation and uterine bleeding. Hamblen's method[7] of cyclic administration is most rational. Oral estrogens are given daily for twenty consecutive days. This is followed by a period of eight or ten days without treatment. If spontaneous bleeding cycles occur, the therapeutic schedule should be adjusted so that treatment is started at the termination of bleeding. If withdrawal bleeding results from estrogen therapy it should either be discontinued or replaced by smaller doses. As a rule, satisfactory *results are obtained with this program which should be continued for two* or three months. If the symptoms remain controlled the dosage should be halved and continued for another two or three months. It is not advisable to continue treatment beyond six months without a rest period for a few months.

Intractable symptoms may require larger doses of estrogens. Intensely psychoneurotic women fall into this category. Where indicated much larger doses may be given but not for longer than five or six weeks. In this type of patient it is often difficult to decide whether the symptoms are genuinely climacteric. Vaginal smear examinations prove very helpful in these instances. When intensive therapy is contemplated its effects should be followed by weekly examinations of smears of the vaginal secretion. In the normal course of estrogen therapy, the characteristic menopausal

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LEGEND FOR FIGURE 58.—(*Continued.*)

A Prior to treatment the smear is of the "atrophic" type. The epithelial cells are immature, originating from the "deep" or "basal" layer of the vaginal mucosa. They are small and thick and have large nuclei. Leucocytes are present in abundance.

B *After 4 days of estrogen administration.* Smear is cleaner as leucocytes diminish in number. Various types of epithelial cells are present ranging in degree of maturity from small young "deep" cells to fully stimulated large thin squamous cells. These are the cornified cells with small pyknotic nuclei.

C After 11 days of therapy (diethylstilbestrol 18 mg.). Almost all the cells are cornified. "Deep" cells are absent and leucocytes are rare. This type of smear represents a full estrogenic effect.

ridge. Not all cases of rudimentary ovaries reported in the literature show true agenesis. Some are of the "arrested development" type which may be associated with tallness of stature rather than shortness and may be due primarily to a lack of pituitary gonadotropic stimulation.

Other manifestations of hypogonadism may be found in the osseous system. Delayed epiphyseal union and osteoporosis are frequent observations. Osteoporosis is evident in the vertebrae and pelvic bones as well as those of the carpus, tarsus and ends of the long bones. Roentgen examination often shows a retardation of bone age by a few years. Anthropometric measurements often reveal a characteristic excess of arm span in comparison to body height. The etiologic relationship of estrogen deficiency to abnormal osseous development has been discussed in a previous section.

Short Stature.—This is to be distinguished from true dwarfism in which the subjects are considerably shorter, usually less than 4 feet in height. Although less than normal in height, patients with ovarian agenesis are generally more than 4 feet tall, averaging about 53 inches.[63] The 11 cases reported by Albright and his collaborators[61] ranged between 53 and 57½ inches. Those of Turner were from 48½ to 57 inches in height.

In some cases the short stature does not become apparent until the pubertal growth spurt fails to occur.[6] In others the history indicates poor growth from the age of seven to ten years. Many explanations have been offered for the shortness of stature in these patients. It is obvious that pure estrogen deficiency *per se* does not account for it. Normal or even increased height is most common in such cases. Furthermore estrogen therapy in patients with ovarian agenesis does not cause appreciable increased growth which might be expected if shortness were due exclusively to an estrogen deficiency. The Albright school favor the theory that secondary changes in adrenocortical function (via altered pituitary stimulation) result in a decreased growth rate. Most other workers[63] regard the growth defect as due not to an endocrine cause but to a basically defective soma which may involve several different tissues or organs of the body. It has been suggested that an associated congenital deficiency of the pituitary growth factor or an end-organ defect may account for statural shortness.[69] The association of multiple congenital anomalies in these patients supports the view that the defect in growth is also congenital in origin. Accepting the theory of multiple congenital germinal defects it does not necessarily follow that each patient with ovarian agenesis must show poor growth. It is conceivable that the substrate for somatic growth may be intact in certain patients with ovarian agenesis. That such is the case is suggested by Meyer's[66] patient who was 66.7 inches tall.

Congenital Abnormalities.—A large variety of associated anomalies have been described and have been reviewed recently by Turner.[63] They are of such frequent occurrence that a diagnosis of ovarian agenesis is not clinically warranted in the absence of at least one demonstrable congenital anomaly. In this way one can usually exclude hypogonadism due to primary pituitary causes as well as that due to the effects of bilateral ovarian disease.

1. Webbing of the neck is probably the commonest anomaly. It consists of a symmetrical winglike fold of skin extending from the base of the

skull to the supraclavicular region resulting in apparent but not real shortening of the neck.[62] Spina bifida may be present in addition to webbing. In 1 case reported from our hospital by Weiner *et al.*[57] webbing was associated with a developmental anomaly of the cervical and other vertebrae and a congenitally absent vagina.

2. Cubitus valgus occurred in all of Turner's original cases and has been found especially frequently in cases reported subsequently. Normally the arm and forearm of the extended limb do not lie in a perfectly straight line. The forearm deviates outward by a few degrees to characterize the normal carrying angle. An exaggeration of this angle is referred to as cubitus valgus and is sometimes the only distinguishing feature of this disease from the point of view of congenital abnormalities.

3. Coarctation of the aorta has been described a number of times and its occurrence in a young or adolescent girl should lead to a prompt investigation of the possibility of associated ovarian agenesis. Ovarian agenesis has been attributed to reduced circulation incidental to aortal coarctation but this can be an etiologic factor, if at all, in only a small minority of instances.

4. Miscellaneous abnormalities include frequent and varied disorders of the eyes and extraocular structures. A peculiar stocky appearance of the chest is rather frequent and has been described as "shield like."[65] The habitus in general is that of a strong, well nourished individual which is in contrast to the frail, thin type seen in pituitary dwarfism. The skin has been characterized in some cases as showing precocious senility and acrocyanosis. Numerous developmental bony abnormalities have also been recorded. These include spina bifida, Klippel-Feil's disease (fusion of vertebrae), syndactylia, talipes and malformed toes, wrists and ribs. Hypertension and congenital heart disease are occasionally present.

Confirmatory Laboratory Data.—Outstanding is the marked increase in urinary gonadotropins, principally of the FSH type. This finding is sufficient by itself to exclude primary pituitary failure and localizes the estrogen deficiency to a primary defect in the ovaries themselves. The urinary neutral 17-ketosteroids are reduced in comparison to subjects of the same age period. However, the excretion of these metabolites is not as markedly reduced or absent as it usually is in panhypopituitarism. The reduced excretion of 17-ketosteroids and the sparse amount of pubic and axillary hair has been interpreted to signify some reduction in adrenocortical function.[64] It is not known whether this represents a direct effect of ovarian insufficiency on the adrenals or whether the effect is mediated through the adenohypophysis. As is to be expected, the urinary excretion of estrogens is reduced. That it is not absent completely is due to the ability of the adrenal cortex to elaborate estrogens. The following case is illustrative of many of the clinical features of this disease.

A fifteen year old Polish born white girl was admitted to the hospital complaining of stunted growth and amenorrhea. There were no siblings nor was there a family history of growth abnormalities. Shortness was first noted at about the age of seven years when it became apparent that she was not as tall as her contemporaries. A heart murmur had been present since birth and her blood pressure two months prior to admission was 190/100. On physical examination

ridge. Not all cases of rudimentary ovaries reported in the literature show true agenesis. Some are of the "arrested development" type which may be associated with tallness of stature rather than shortness and may be due primarily to a lack of pituitary gonadotropic stimulation.

Other manifestations of hypogonadism may be found in the osseous system. Delayed epiphyseal union and osteoporosis are frequent observations. Osteoporosis is evident in the vertebrae and pelvic bones as well as those of the carpus, tarsus and ends of the long bones. Roentgen examination often shows a retardation of bone age by a few years. Anthropometric measurements often reveal a characteristic excess of arm span in comparison to body height. The etiologic relationship of estrogen deficiency to abnormal osseous development has been discussed in a previous section.

Short Stature.—This is to be distinguished from true dwarfism in which the subjects are considerably shorter, usually less than 4 feet in height. Although less than normal in height, patients with ovarian agenesis are generally more than 4 feet tall, averaging about 58 inches.[63] The 11 cases reported by Albright and his collaborators[64] ranged between 55 and 57[1] inches. Those of Turner were from 48½ to 57 inches in height.

In some cases the short stature does not become apparent until the pubertal growth spurt fails to occur.[64] In others the history indicates poor growth from the age of seven to ten years. Many explanations have been offered for the shortness of stature in these patients. It is obvious that pure estrogen deficiency *per se* does not account for it. Normal or even increased height is most common in such cases. Furthermore, estrogen therapy in patients with ovarian agenesis does not cause appreciable increased growth which might be expected if shortness were due exclusively to an estrogen deficiency. The Albright school favor the theory that secondary changes in adrenocortical function (via altered pituitary stimulation) result in a decreased growth rate. Most other workers[63] regard the growth defect as due not to an endocrine cause but to a basically defective soma which may involve several different tissues or organs of the body. It has been suggested that an associated congenital deficiency of the pituitary growth factor or an end-organ defect may account for statural shortness.[63] The association of multiple congenital anomalies in these patients supports the view that the defect in growth is also congenital *in origin*. *Accepting the theory of multiple congenital germinal defect*, it does not necessarily follow that each patient with ovarian agenesis must show poor growth. It is conceivable that the substrate for somatic growth may be intact in certain patients with ovarian agenesis. That such is the case is suggested by Meyer's[64] patient who was 60.7 inches tall.

Congenital Abnormalities.—A large variety of associated anomalies have been described and have been reviewed recently by Turner.[64] They are of such frequent occurrence that a diagnosis of ovarian agenesis is not clinically warranted in the absence of at least one demonstrable congenital anomaly. In this way one can usually exclude hypogonadism *due to* primary pituitary causes as well as that due to the effects of bilateral ovarian disease.

1. Webbing of the neck is probably the commonest anomaly. It consists of a symmetrical winglike fold of skin extending from the base of the

neutral 17 ketosteroids was low being 1 2 mg per twenty four hours (average normal for this age period would be 5 or 6 mg) The 11-oxycorticosteroids were excreted in normal amounts (1 02 mg per twenty four hour volume) Roentgen examination showed no abnormality of the sella turcica the visual fields were normal and the glucose tolerance test was within normal limits The basal metabolic rate was not subnormal A thorough cardiologic investigation established the presence of coarctation of the aorta This was indicated by hypertension reduced oscillometric readings in the lower extremities arterial pulsations over the back medial to the scapular region and notching with erosions of the lower margins of several ribs The nature of the aortal lesion was definitely confirmed by angiocardiographic studies

In summary this patient presented statural shortness undeveloped genitalia and breasts amenorrhea webbing of the neck and increased urinary gonadotropins The complete absence of pubic and axillary hair is not a usual finding but is consistent with the markedly depressed urinary level of neutral 17 ketosteroids

Treatment —Since the ovaries are intrinsically deficient they are generally incapable of stimulation Hence, therapy must be of the substitution type and involves the use of estrogenic substances in full replacement doses The need for long term therapy makes the oral route preferable Daily doses of diethylstilbestrol 1 mg sodium estrone sulphate 1 25 mg or ethinyl estradiol 0 1 mg may be adequate for this purpose although no hard and fast rules for dosage can be formulated The dosage should be regulated according to the clinical effects produced Therapy should be cyclic in that an effort should be made to simulate the variations in estrogen levels that occur under normal physiologic conditions Oral estrogens administered for 20 consecutive days out of every twenty-eight or thirty days accomplish this purpose Large doses may induce cyclic uterine bleeding which may or may not be objectionable If desired this can be avoided by reducing the dose of estrogen

If for any reason parenteral therapy is employed similar results may be obtained by the intramuscular injection of a total of 50 000 rat units of estradiol benzoate during the first half of each month This may be given as 10 000 rat units or 1 66 mg every third day

As a result of estrogen therapy fairly normal development of the uterus vagina breasts and pubic and axillary hair can be obtained No significant effect on body height occurs Since these patients remain permanently sterile the goal of therapy should be optional with the patient Most patients will be satisfied and quite gratified if only the external manifestations of feminity are acquired *i e* breast and pubic hair development Enlargement of the uterus serves no purpose but an increase in the volume of the vagina becomes an important consideration in the event of marriage

Estrogenic Failure Due to Panhypopituitarism —Conditions in which there is a decrease in the several tropic functions of the adenohypophysis produce ovarian failure along with insufficiency of the other target-organs Total involvement of the secretory function of the anterior lobe of the pituitary gland (Simmonds disease) is described at length in the chapter dealing with this gland Pertinent to the present discussion is the fact that secondary female hypogonadism is usually readily distinguishable

her appearance was that of a short girl with a prominent chest showing webbing of the neck and no breast development The nipples were inverted and the configuration of the thorax was "shield like" in that its prominence was due to an increased anterior and transverse diameter Cubitus valgus was absent There was no axillary, pubic or body hair and none was present on the extremi-

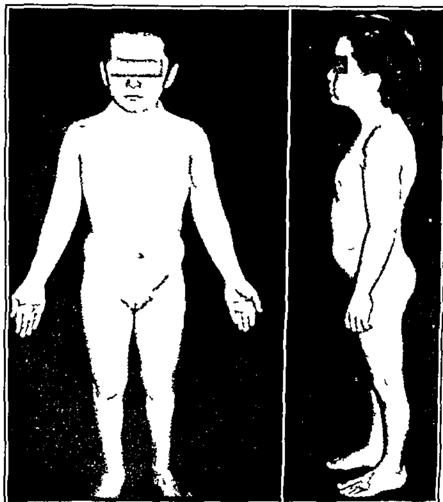


FIG 59 —Ovarian agenesis A 15 year old girl 49 inches tall showing webbing of the neck complete absence of pubic and axillary hair undeveloped breasts and shield like configuration of the thorax The assay for urinary gonadotropins was positive at 240 m u u per 24 hours

ties The external genitalia were infantile and the hymen was intact By rectal examination only a thickened ridge could be felt instead of a cervix and uterus The adnexae could not be defined A roentgen survey of all the bones revealed no abnormality of bone or calcification The long bones were simply shorter than what was to be expected at her stated age The urinary gonadotropins during a twenty four hour period were markedly elevated, a positive mouse uterine reaction being obtained at 240 units (the upper limit of normal is regarded as 40 to 50 mouse uterine units by the method employed in our laboratory a modification of the Klinefelter Albright and Griswold[70] and Smith Albright and Dodge[71] methods) The urinary excretion of

is complicated by uterine hemorrhage. As a result of the transient circulatory collapse, ischemic changes are produced in the adenohypophysis. These may range in severity from the mildest form which causes no symptoms to the severe type characterized by a total loss of hormone function (Simmonds' disease). In between these two extremes may be found clinical states distinguished by a decreased function of one or more adenohypophyseal tropic hormones. Involvement of the gonadotropic function results in persistent postpartum secondary amenorrhea. Varying grades of thyroid and adrenocortical insufficiency are often present as a result of decreased thyrotropic and adrenocorticotropic function.

In addition to a case described elsewhere in this book (p. 127) the following case 11 of Klinefelter and his coworkers[0] is briefly summarized:

> A thirty-eight year old woman was amenorrheic since her second childbirth nine years previously. Delivery was complicated by a profuse uterine hemorrhage. A loss of axillary and pubic hair was noted and a marked anemia was present. The basal metabolic rate was −23 per cent, the serum cholesterol 367 mg per cent and the urinary excretion of neutral 17-ketosteroids less than 0.5 mg in twenty four hours. These findings indicated reduced thyroid and *adrenocortical function. The insulin tolerance test revealed a characteristic* hypoglycemia unresponsiveness. Roentgen examination showed no abnor*mality of the sella turcica.* Urinary gonadotropin excretion was low, being less than 6.6 mouse uterine units. However, note is made of the fact that the patient was receiving methyltestosterone which is capable of suppressing pituitary gonadotropic secretion.

Estrogenic Failure Due to Relative Hypopituitarism.—Certain instances of hypogonadism in the female, as well as the male, are due to a selective deficiency of pituitary gonadotropic function. These individuals manifest *no significant disturbance of the thyroid, adrenals or pancreas* but show hypogonadotropic ovarian insufficiency. As in the case of panhypopituitarism, urinary assays reveal very low or absent titers of gonadotropins. Low urinary *excretion values for 17-ketosteroids are frequently encount*ered but these may be attributed to malnutrition or general debility.[59] A secondary effect of estrogenic failure on adrenocortical activity may also contribute to a decreased elimination of 17-ketosteroids in some patients.

Partial pituitary failure may be due to rare instances of Frohlich's syndrome in which the hypothalamico-pituitary pathways are affected. In some instances it may be due to the Laurence-Moon-Biedl syndrome which is also characterized by hypogonadism and obesity. In addition these patients show several associated congenital abnormalities such as retinitis pigmentosa, polydactylism and mental deficiency.[74] In some instances isolated deficiency of pituitary gonadotropic secretion may represent a relatively mild example of Sheehan's syndrome. The history in these patients is characteristic in that secondary amenorrhea developed and persisted after childbirth. Close questioning usually discloses the fact that a uterine hemorrhage, often so mild as to have been forgotten, occurred during or shortly after parturition. In the majority of cases where the onset of selective hypopituitarism occurs prepuberally, no etiologic factor is ascertainable.

When selective pituitary gonadotropic failure begins before the completion of puberty, abnormal skeletal changes often appear in the adult which

from instances of estrogenic failure due to primary intrinsic disease of the ovaries

The onset of complete pituitary deficiency *prior to the completion of puberty* results in significant skeletal and genital changes. It usually produces so-called pituitary dwarfism. The short stature is due to the absence of pituitary growth hormone during the formative years of childhood. These patients usually measure less than 4 feet in height and are therefore usually smaller than those with ovarian agenesis. In addition the genitalia and breasts remain infantile and primary amenorrhea is the rule. There is virtually no hair growth on the body and pubic and axillary hair are absent.

A case cited by Klinefelter, Albright and Griswold [69] as case 15 of their series illustrates several characteristic features of hypogonadism due to panhypopituitary dwarfism.

> A twenty four year old woman weighing 60 pounds was 49.6 inches tall. The arm span was considerably greater than the height. It had been noticed that growth was not normal since the age of three years. The general appearance was that of a ten year old child and she complained of general weakness. Sexual development was absent. She disliked cold weather and the basal metabolic rate was −23 per cent. The urinary excretion of neutral 17 ketosteroids was extremely low, *being less than 0.5 mg in twenty four hours*. Urinary gonadotropins were very low and could not be demonstrated when tested at levels of 6.6 and 3.3 mouse uterine units. (These results are inconclusive because the patient was receiving estrogen therapy at the time which may possibly depress pituitary gonadotropic activity.) The insulin tolerance test disclosed a characteristic unresponsiveness to induced hypoglycemia.[2] Roentgen examination showed a retarded bone age but there was no abnormality of the sella turcica.

Postpuberal panhypopituitarism (true Simmonds' disease) results in no skeletal abnormalities. Regressive changes appear in the genitalia and breasts, pubic and axillary hair become sparser and secondary amenorrhea supervenes. Sterility is absolute.

Regardless of whether pituitary failure begins before or after puberty the urinary excretion of neutral 17 ketosteroids, estrogens and androgens is very low. These substances are formed and excreted in even smaller amounts than they are in patients with primary ovarian deficiency. This is due to associated failure of the adrenal cortex, normally an important source of steroid hormone production. Decreased pituitary function is also revealed by the insulin tolerance test which usually shows a characteristic unresponsiveness to insulin induced hypoglycemia. This is characterized by a slow return of the blood sugar to normal after hypoglycemia is induced by the intravenous administration of insulin.

Urinary gonadotropins are either very low or absent. In 14 female and male individuals suffering from this disease Klinefelter and his collaborators[70] found the urinary gonadotropin titer to be less than 6.6 mouse uterine units in twenty four hours. The lower limit of normal by their method is a positive test at 6.6 units.

It is not intended to engage in a detailed description of panhypopituitarism but one type is particularly appropriate to the present discussion. This is the syndrome described by Sheehan[3] and often referred to as Sheehan's syndrome. It occurs soon or sometime after parturition which

is complicated by uterine hemorrhage. As a result of the transient circulatory collapse ischemic changes are produced in the adenohypophysis. These may range in severity from the mildest form which causes no symptoms to the severe type characterized by a total loss of hormone function (Simmonds' disease). In between these two extremes may be found clinical states distinguished by a decreased function of one or more adenohypophyseal tropic hormones. Involvement of the gonadotropic function results in persistent postpartum secondary amenorrhea. Varying grades of thyroid and adrenocortical insufficiency are often present as a result of decreased thyrotropic and adrenocorticotropic function.

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menstruation involves a delicate interplay between ovarian and pituitary hormones and a sensitive endometrial reactivity to the ovarian hormones it is easy to understand that a disturbance at any of these levels may cause irregular uterine bleeding. Furthermore, such factors as the general state of physical and mental health also contribute to the regulation of periodicity. Therefore, many remote extra-endocrine conditions may also be responsible for disturbances of the menstrual rhythm.

The present discussion centers about those disorders of uterine bleeding which are not due to actual organic disease of the pelvic viscera or to manifest endocrine disease. The former properly belong in the domain of straightforward gynecology. The latter constitute the principal subject matter of the present chapter. Endocrine disturbances characterized by ovarian failure have already been described in the form of clinical diseases or syndromes. Awaiting discussion are the endocrine diseases distinguished by excessive estrogen formation. These are comprised mainly of certain estrogen-producing ovarian tumors and estrogen-producing persisting ovarian follicles.

After separation of conditions due to forthright endocrine and local pelvic diseases there still remains a large number of menstrual disorders ranging from amenorrhea to excessive uterine bleeding. Every imaginable type of variation in periodicity and amount of flow may be found. These are the so-called functional disorders of menstruation and, strictly speaking, they are also based on a disturbance in hormonal relationships and endocrine balance. However, the underlying endocrine disturbances are so subtle that they are generally not readily recognized or demonstrated without the assistance of highly technical laboratory procedures such as endometrial biopsy or hormonal assay. Furthermore, not all minor disturbances of menstruation lend themselves to endocrine interpretation capable of substantiation. Even when laboratory tests in these cases suggest a particular type of hormonal disturbance, therapeutic attempts at correction often fail or meet with indifferent success. The mere multiplicity of hormonal therapeutic regimes currently in vogue attests to the unsatisfactory state of our knowledge of the fundamental mechanisms involved in many menstrual disorders. These comments are not to be construed as indicative of diagnostic or therapeutic nihilism. Rather do they explain the reasons for excluding certain pathophysiologic phenomena from the scope of this book. For similar reasons, therefore, it is not intended to include discussions of general menstrual irregularities, dysmenorrhea, infertility and complications of pregnancy and the puerperium. Detailed analyses of these subjects are available in several standard and authoritative books.[6,7,9,48]

Ordinarily included in the array of "functional" disturbances of uterine bleeding is one which is a distinct endocrine entity. It is a special type of functional uterine bleeding which is due to a definitive pathophysiologic condition of the ovaries and is usually accompanied by a characteristic alteration of the endometrium. For these reasons it may be regarded as an endocrine disease.

Functional Uterine Bleeding.—This is a term applied to abnormal bleeding which is not due to organic disease although it may be associated with it. It is always characterized by an excessive flow. If it occurs with regu

are reminiscent of the eunuchoidal state in men. The individual may grow excessively tall because of delay in epiphyseal closure of the long bones. This permits the long bones to grow over a longer period of time than normally. As a result the arm span exceeds the body height. In addition there are the usual stigmas of prepuberal estrogen deficiency. These include failure of genital and breast development, primary amenorrhea and a sparse or normal growth of axillary and pubic hair. Sexual hair is not apt to be completely absent as it is in prepuberal panhypopituitarism. This is because of the preservation of adrenocortical function which partially regulates pubic and axillary hair growth.[61]

Case 35 of the previously mentioned series[9] serves to illustrate some of the clinical features of patients with primary amenorrhea due to idiopathic lack of pituitary gonadotropins.

A twenty-one year old young woman showing a complete lack of secondary sexual development was 65 inches tall and had an arm span which was 2 inches in excess of her height. There was no breast development and the vagina was infantile, although the clitoris was normal. Body, pubic and axillary hair was normal, having appeared at the age of fourteen years. Peritoneoscopy showed normally sized inactive ovaries and infantile uterus and tubes. Retardation of bone age and a normal sella turcica were noted by roentgen examination. The urinary excretion of neutral 17 ketosteroids was somewhat reduced, measuring 4.4 and 5.8 mg per twenty four hours. The assay for urinary gonadotropins was negative at 6.6 mouse uterine units, which represents a low titer.

The development of selective gonadotropic deficiency after the completion of puberty results primarily in secondary amenorrhea. If the condition persists long enough, some genital and breast regression may be noted. Most patients in this category are those suffering from debilitating systemic diseases which secondarily inhibit pituitary activity. These include chronic renal and tuberculous disease, diabetes mellitus and adrenocortical and thyroid disease. The exogenous administration of large doses of estrogens and androgens over protracted lengths of time also produces secondary ovarian deficiency. Infertility and usually secondary amenorrhea result, but in the case of excessive estrogen administration there is, of course, no regression of the breasts or accessory genitalia. It is quite possible that gonadal insufficiency in arrhenoblastoma of the ovary (a tumor which often has masculinizing effects) may be mediated via pituitary gonadotropin suppression.

Treatment of estrogen deficiency occurring secondarily to pituitary failure is usually satisfactory only when it is based on estrogen replacement. Ideally, gonadotropin therapy would be the most natural way of dealing with these patients. Unfortunately, potent and purified gonadotropin extracts capable of producing effective clinical results are limited and unsatisfactory. This subject has been discussed in detail in a previous section, p. 639. Wherever possible, factors which may be exerting a secondary suppressive effect on the adenohypophysis should be removed.

Functional Disturbances of Uterine Bleeding. — Although the majority of normal women menstruate at fairly regular intervals ranging between twenty six and thirty days, a great number and variety of menstrual irregularities are encountered clinically. Since the phenomenon of normal

also at times result from ovarian hypofunction. With the aid of serial vaginal smear examinations a persistently high percentage of cornified cells is usually found in patients with *functional uterine bleeding*. This is indicative of a continuously increased estrogen secretion by the persistent follicles and its demonstration during periods of amenorrhea is quite characteristic. On the other hand a certain number of patients having endometrial hyperplasia on biopsy examination show evidence of subnormal estrogenic stimulation. This is indicated by vaginal smears containing uniformly low cornification of the vaginal epithelial cells. In Shorr's opinion endometrial hyperplasia may develop in patients with ovarian hypofunction as a result of incomplete or absent endometrial shedding during anovulatory cycles. In this way the endometrium is permitted to become more and more developed under the influence of continuous low grade estrogenic stimulation. Under these circumstances continuous proliferation eventuates in true endometrial hyperplasia and the end result is the same as that produced by continuously high levels of estrogen.

In the typical case of functional uterine bleeding the ovaries contain Graafian follicles in various stages of development. The number of follicle cysts in each ovary ranges from a few to as many as 25 to 30 of which many are atretic. Corpora lutea are absent.[8]

The diagnosis of functional uterine bleeding is essentially made by exclusion. Its relatively frequent occurrence in the postmenarchal girl is usually not much cause for concern. Nevertheless a careful diagnostic investigation for pelvic or general endocrine disease should be carried out. In addition to a competent appraisal of the gynecologic status of the patient the normality of sexual and physical maturity should be ascertained. The possibility of thyroid dysfunction, blood dyscrasia or estrogen producing ovarian tumor must be excluded. Rarely diagnostic curettage is indicated since uterine cancer is not unknown during the third decade of life.[31]

In women past the second decade of life vaginal smears should be examined for cytologic evidence of malignancy. If these are negative it is always important to employ complete uterine curettage with histologic examination of the curettings. Only by this means can one be certain that the bleeding is not due to some organic intrauterine cause. Hormone assays and evaluations of ovarian function by serial vaginal smear examination may support the clinical impression of functional bleeding but should not replace tissue examination as a diagnostic measure.

Treatment of functional uterine bleeding is often not required. This is particularly true in adolescent girls when mild forms of excessive bleeding often abate spontaneously. On the other hand profuse or prolonged bleeding in women who are approaching or actually experiencing the climacteric is always to be viewed with suspicion. While such flowing may be physiologic in that anovulatory cycles commonly occur during this era it is also true that organic causes usually prevail at this time.[7] The therapeutic approach therefore is somewhat different depending upon the age of the individual and the need for preserving reproductive function. Regardless of these considerations brisk and alarming hemorrhage always requires curettage. At times blood transfusion may be necessary to overcome the result

larity, it may merely accentuate the menstrual flow and is known as *menorrhagia*. Its occurrence at intervals between the menses produces *metrorrhagia*, while a combination of the two is called *menometrorrhagia*. Bleeding may occur after episodes of amenorrhea and may be mistaken for abortion. The bleeding may be continuous, profuse and alarming, leading to marked secondary anemia.

Functional uterine bleeding occurs most often in the premenopausal stage or adolescence. About one third of the cases are distributed uniformly throughout the intervening years of reproductive activity.[48]

Its high incidence at the extremes of reproductive life coincides with the ages at which women are most likely to have anovulatory cycles. An etiologic relationship between lack of ovulation and excessive bleeding was established by histopathologic correlations between the ovaries and endometrium made by Schroeder[51] in 1915. This worker showed that certain cases of excessive uterine bleeding, which he termed *metropathia hemorrhagica*, were due to the abnormal persistence of unruptured Graafian follicles. The continued secretion of estrogen by the latter results in excessive proliferation of the endometrium. This is an abnormal endometrium in two respects. Firstly, there is an absence of secretory development since unruptured follicles do not produce corpora lutea. Secondly, the continued estrogenic stimulation causes a true endometrial hyperplasia over and above the normal estrogenic proliferative phase. This type of endometrial hyperplasia is known as 'swiss cheese' hyperplasia because of the large number of irregularly sized glands, many of which are dilated and cystic. When regression of this hyperplastic highly vascularized endometrium occurs, resulting bleeding is almost necessarily profuse. However, extreme hyperplasia may exist for prolonged periods without breaking down, accounting for antecedent *amenorrhea* in many cases. The mechanisms underlying the final disintegration of the hyperplastic endometrium are not known. An ultimate waning of secretory activity on the part of the unruptured follicles may produce a withdrawal effect. It is also believed that progesterone deficiency may play a role in the bleeding.[6]

Novak[48] is of the opinion that most cases of functional uterine bleeding are to be explained on the basis of estrogen withdrawal. However, it is to be emphasized that abnormal flowing can occur from almost any type of endometrium, so that this mechanism does not always hold. Endometrial biopsy at the onset of bleeding may show an atrophic endometrium, or one in a proliferative or secretory phase. In a small minority of cases the endometrium may be of the 'mixed type', showing both proliferative and secretory changes in different areas. Statistically, Mazer and Israel[5] found hyperplasia in 67.7 per cent, a purely proliferative phase in 17.7 per cent, atrophy in 9.3 per cent and a secretory phase in 5.3 per cent of 96 patients. A more or less similar distribution of endometrial findings were reported by Jones and TeLinde.[6] Hyperplastic endometrium was observed in 75 per cent, proliferative phase in 18.4 per cent, secretory phase in 4.4 per cent and atrophy in 2.2 per cent of 92 cases.

Although endometrial hyperplasia is found in the majority of patients with functional bleeding and is generally indicative of hyperestrogenism, it appears from the studies of Shorr[3] that this endometrial condition may

do at times result from ovarian hypofunction. With the aid of serial vaginal smear examinations a persistently high percentage of cornified cells is usually found in patients with *functional uterine bleeding*. This is indicative of a continuous or increased estrogen secretion by the persistent follicles and its demonstration during periods of amenorrhea is quite characteristic. On the other hand a certain number of patients having endometrial hyperplasia on biopsy examination show evidence of subnormal estrogenic stimulation. This is indicated by vaginal smears containing uniformly low cornification of the vaginal epithelial cells. In Shorr's opinion endometrial hyperplasia may develop in patients with ovarian hypofunction as a result of incomplete or absent endometrial shedding during anovulatory cycles. In this way *the endometrium is permitted to* become more and more developed under the influence of continuous low grade estrogenic stimulation. Under these circumstances continuous proliferation eventuates in true endometrial hyperplasia and the end result is the same as that produced by continuously high levels of estrogen.

In the typical case of functional uterine bleeding the ovaries contain Graafian follicles in various stages of development. The number of follicle cysts in each ovary ranges from a few to as many as 25 to 30 of which many are atretic. Corpora lutea are absent.[1]

The *diagnosis of functional uterine bleeding* is essentially made by exclusion. Its relatively frequent occurrence in the postmenarchal girl is usually not much cause for concern. Nevertheless a careful diagnostic investigation for pelvic or general endocrine disease should be carried out. In addition to a competent appraisal of the gynecologic status of the patient the normality of sexual and physical maturity should be ascertained. The possibility of thyroid dysfunction, blood dyscrasia or estrogen producing ovarian tumor must be excluded. Rarely diagnostic curettage is indicated since uterine cancer is not unknown during the third decade of life.[65]

In women past the second decade of life vaginal smears should be examined for cytologic evidence of malignancy. If these are negative it is always important to employ complete uterine curettage with histologic examination of the curettings. Only by this means can one be certain that the bleeding is not due to some organic intrauterine cause. Hormone assays and evaluations of ovarian function by serial vaginal smear examination may support the clinical impression of functional bleeding but should not replace tissue examination as a diagnostic measure.

Treatment of functional uterine bleeding is often not required. This is particularly true in adolescent girls when mild forms of excessive bleeding often abate spontaneously. On the other hand profuse or prolonged bleeding in women who are approaching or actually experiencing the climacteric is always to be viewed with suspicion. While such flowing may be physiologic in that anovulatory cycles commonly occur during this era it is also true that organic causes usually prevail at this time.[2] The therapeutic approach therefore is somewhat different depending upon the age of the individual and the need for preserving reproductive function. Regardless of these considerations brisk and alarming hemorrhage always requires curettage. At times blood transfusion may be necessary to overcome the result

ing menia By removing the usually hyperplastic endometrium a temporary cure is often effected On the other hand this procedure may disclose the presence of organic intrauterine disease which results in an alteration of the diagnosis

In younger patients conservative therapy is employed since it is desirable to preserve reproductive capacity For this reason, radiotherapy is not given and hormonal agents are administered The management of the older patient depends largely upon whether or not she is desirous of bearing children If reproductive function is not a consideration, radiotherapy is the procedure of choice, the particular modality depending again upon the age of the individual Since roentgentherapy destroys ovarian function it results in menopause and is preferably employed in women over the age of forty five years In younger subjects premature climacteric and its possible attendant discomfort can be avoided by the intrauterine application of radium This acts only on the endometrium and does not produce estrogen withdrawal symptoms At the risk of repetitiousness it is to be emphasized that neither radiotherapy nor endocrine therapy should be instituted until after thorough pelvic examination and diagnostic curettage with microscopic examination have been performed As previously mentioned the latter procedure can often be safely dispensed with in postmenarchal girls

Various types and combinations of hormonal agents are employed in the treatment of women to whom the possibility of future pregnancy is an important consideration The mere fact that there are several different effective hormonal regimens indicates that the underlying etiologic mechanisms are not definitely known or at best poorly understood The lack of a uniform system of management is exemplified by the following array of hormonal substances which are currently used singly and in combination estrogen progesterone estrogen progesterone androgen and androgen progesterone Each type of therapy has its ardent advocates claiming effective results with its use The rationale for estrogen therapy is based on eliminating the estrogen withdrawal element in endometrial regression By keeping estrogen levels above the so called bleeding level bleeding can usually be stopped However estrogens must then be reduced very gradually in order to avoid a return of severe bleeding The use of progesterone therapy is based on the fact that as a result of anovulation corpora lutea are absent in the majority of cases These patients therefore have a progesterone deficiency and the administration of this hormone is intended to produce a normal secretory endometrium after the hyperplastic mucosa is shed The basis for androgen *therapy lies in its ability to inhibit ovarian function thereby* lessening follicular hypersecretion of estrogens and endometrial hyperplasia

Estrogens are preferred by Hamblen[7] who has devised a rational schedule of therapy which has been used with considerable success The administration of large doses during the stage of hemorrhage usually arrests the flow in a few days This is accomplished by daily doses of 6 mg of diethylstilbestrol 7 5 mg of sodium estrone sulphate or 0 6 mg of ethinyl estradiol If bleeding is not curtailed in a few days doses may be increased by 25 to 100 per cent After bleeding has stopped the same dosage is continued for twenty consecutive days in an effort to produce bleeding cycles of normal

periodicity and amount. Withdrawal bleeding usually occurs one to five days after discontinuing estrogens. On the fifth day of withdrawal bleeding or seven days after the cessation of therapy if no withdrawal bleeding occurs, another series of twenty daily doses of estrogen is administered followed by a week or ten days *of no treatment*. *A third course of therapy* given in one half the original dose is usually effective in regulating the cycles and preventing excessive bleeding.[7] If bleeding occurs at any time during therapy, estrogens should be discontinued and another series started on the fifth day of bleeding.

Progesterone is advocated by many workers.[7, 47, 77, 78] It is given for two separate purposes: first, to control the immediate bleeding phase and second to restore normal menstrual cycles. For the treatment of active hemorrhage, 10 to 20 mg. in oil are injected intramuscularly daily for four to six days. Orally active anhydrohydroxyprogesterone may be given in 40 to 80 mg. daily doses instead. This brief course of intensive therapy does not always arrest the bleeding promptly. In fact in some instances hemorrhage may become very profuse, a possibility of which the patient should be forewarned. This is due to sudden endometrial disintegration, a veritable "medical curettage."[7] Even if bleeding stops during therapy, it will be followed again in a few days by a short phase of bleeding as a progesterone withdrawal effect. In any case, a cessation of bleeding is to be anticipated in a week or two after discontinuing therapy. Normal menstrual cycles may be resumed after this initial course of progesterone therapy, especially if a "curettage effect" is produced. This corresponds to what frequently occurs after surgical curettage.

In many cases, however, it is advisable to resort to cyclic progesterone therapy if the initial intensive course fails to restore normal menstrual cycles. A variety of treatment schedules have been offered by workers in this field, differing largely in dosage and timing. Essentially they consist of the administration of corpus luteum hormone parenterally or orally during the latter stages of an intermenstrual phase, stopping two or three days before the expected flow. Progesterone 5 or 10 mg. is injected every other day for 4 doses starting on the twentieth day after the onset of menstruation or withdrawal bleeding. Anhydrohydroxyprogesterone 10 or 20 mg. daily by mouth for a week serves as a satisfactory alternate to parenteral therapy.

From the point of view of simulating normal physiologic conditions, a *combined* course of estrogens and progesterone is recommended. This is simply accomplished by giving oral estrogens as outlined above for twenty days and adding progesterone on the sixteenth day of estrogen treatment for about a week or ten days. Under these circumstances the most satisfactory results are obtained with daily doses of diethylstilbestrol 3 mg., sodium estrone sulphate 3.75 mg. or ethinyl estradiol 0.3 mg. Progesterone is injected every other day in 10 mg. quantities for 4 or 5 doses. The equivalent oral dose of anhydrohydroxyprogesterone is 20 mg. daily.

Androgens are favored by some clinicians who find it superior to other forms of hormonal therapy.[43, 80, 142] The male sex hormone exerts its effect on the uterus in two ways. By its suppressive action on the pituitary, ovarian function is inhibited and the endometrium is allowed to involute

In addition, androgens neutralize estrogenic effects directly at the endometrial level[52] It is thus possible to terminate the active bleeding phase Its subsequent use can be planned to inhibit bleeding altogether for a few months in the hope that when it recurs after cessation of therapy it will be of the normal menstrual type

The use of androgens in women is attended by the possibility of undesirable masculinizing effects In general however relief of the functional bleeding can usually be obtained with doses lower than those which induce virilization[50] A total monthly dosage of less than 250 or 300 mg of testosterone propionate or 700 to 800 mg of methyltestosterone may achieve a therapeutic effect and not cause arrhenomimetic signs This can be accomplished by the parenteral administration of 25 mg of testosterone propionate every three or four days or the oral administration of 25 mg of methyltestosterone daily Dosages larger than these are prone to result in the development of hirsutism hoarseness with lowering of voice pitch acne enlargement of the clitoris increased libido and an annoying vaginal discharge While most of these effects are reversible after therapy is discontinued, hair growth and laryngeal changes may persist

However it is to be emphasized that dosages reported to be effective in the relief of functional bleeding have been quite variable The *active* bleeding phase usually ceases after 4 or 5 intramuscular injections of 25 mg of testosterone propionate in oil every other day An equivalent response may be obtained by the oral administration of a 25 mg tablet of methyltestosterone twice daily for a week or ten days When bleeding has stopped androgens may be continued with the idea of preventing all bleeding for a few cycles This gives the endometrium an opportunity to rest so that normal ovarian endometrial relationships can be resumed after discontinuation of therapy

It is a matter of interest that significant modification of normal menstrual cycles usually requires a minimum monthly dosage of 300 to 500 mg of testosterone propionate[53,54] At these dose levels evidences of masculinization are apt to occur in an appreciable percentage of patients It is most fortunate therefore that in women with functional bleeding therapeutic success may be obtained with subarrhenomimetic doses (150 to 250 mg of testosterone propionate per month) The fact that small doses (less than 250 mg) affect bleeding in these patients while they are ineffective in this respect in women with normal menstrual cycles may be due to the synergistic effect on the pituitary of the existing higher levels of estrogen

In view of the uncertainties and limitations inherent in androgen therapy it hardly seems desirable to use it in preference to estrogen and/or progesterone treatment The latter is equally effective and lacks the hazards of defeminization or masculinization

Ovarian Tumors Accompanied By Endocrine Manifestations — The ovaries like the other endocrine glands are frequently involved by neoplasia New growths of the ovaries may be asymptomatic or may produce the conventional symptomatology characteristic of tumors in general In certain instances however ovarian tumors may be associated with alterations in the hormonal status of the individual Endocrine manifestations

in most of these cases are due to a secretory function of the tumor itself which has a profound effect on the general soma and sexual apparatus. These are the feminizing and masculinizing tumors. A non-sexual but general systemic endocrine disturbance is produced by the hyperfunctioning ovarian struma, a rare cause of hyperthyroidism. There is another ovarian tumor which is not known to be hormone-producing but is nevertheless often associated with maldevelopment of the genital system. This is the dysgerminoma which in rare instances is also accompanied by minor evidences of virilization.

Mechanisms underlying the development of this interesting group of tumors and their assumption of secretory function are poorly understood. Many divergent theories have been advanced, most of which are inadequately substantiated by fact. Several factors are contributory to our limited knowledge in this respect. Uncertainties concerning the histogenesis of the normal anatomic elements of the ovary make it difficult to evaluate the histogenesis of tumors. The problem of tumorigenesis is further complicated by difficulties in distinguishing primarily ovarian neoplasms from those appearing to arise from ectopic cellular inclusions such as adrenal cortical rests. The frequent lack of uniform cytologic characteristics occasionally renders precise histologic diagnosis difficult, if not equivocal. For these reasons no one classification of ovarian tumors, especially of the endocrine variety, is universally acceptable to all workers in this field.

From a practical point of view the most satisfactory tabulation is one based by Novak[85] on a mixture of criteria. These include a consideration of known or suspected histogenesis, pathologic findings and clinical data. Other satisfactory working categorizations are those of Geist,[86] Barzilai[87] and Selye.[88] The need for evaluating clinical data in the final interpretation of a pathologic lesion attests to the inadequacies of strict morphologic diagnosis. However, until such time as precise histogenetic and hormonologic relationships become incontrovertibly established, this is the most effective way of dealing with the nosology of ovarian tumors. Data derived from hormonal assays of tumor tissue and from the body fluids of patients are unfortunately very meager. This is due principally to the relative scarcity of clinical material and the frequent lack of facilities for complete hormonal study. An additional difficulty is the infrequency with which certain endocrine ovarian tumors are diagnosed pre-operatively. This applies particularly to the feminizing group of tumors occurring in the adult before the menopause where abnormal feminizing effects are usually not very apparent. It is to be hoped that the more extensive application of the newer methods of hormone assay to tumor tissue and to patients' blood and urine before and after operation will help elucidate some of the more subtle mechanisms involved in the subject under discussion.

Ovarian tumors associated with endocrine manifestations are quite uncommon, constituting less than 2 per cent of all ovarian tumors. In most instances these tumors are hyperfunctional in the sense that they elaborate an excessive amount of hormones. When these are predominantly of the estrogenic type, the tumors produce the effects of hyperestrogenism or feminization. An excessive quantity of androgenic hormone secretion re-

sults in masculinizing effects. Rarely, the ovary develops a hyperfunctioning thyroid tumor of teratomatous origin, which causes the clinical manifestations of hyperthyroidism. Lastly, there is a tumor believed to be nonfunctional which is, nevertheless, occasionally accompanied by endocrine disturbances. This is the dysgerminoma. For the present the various endocrine tumors of the ovary may be grouped as follows:

1. Feminizing tumors (granulosa cell, theca cell and their luteinized forms *comprising one type of luteoma*)
2. Masculinizing tumors (arrhenoblastoma, "hilus cell" tumor and a controversial group comprising adrenal rest tumor, luteoma, masculinovoblastoma and "virilizing lipoid cell" tumor)
3. Struma ovarii
4. Dysgerminoma

Feminizing Tumors.—This is a group of neoplasms distinguished by their ability to produce evidences of excessive estrogenic stimulation in *the patient. Forming this group are the granulosa cell and theca cell* tumors. These may exist as "pure" forms of each or very often as tumors containing the granulosal epithelial elements characteristic of the former combined with the thecal connective tissue qualities of the latter. Just as luteinization of granulosal and thecal cells occurs in the normal ovarian follicle, so may tumor growths of these cells appear luteinized. This results in a transformation into evidently typical lutein cells with the formation of one type of luteoma.[85]

All workers in this field are not in agreement as to the histogenesis of these tumors or their separate identities. For example, Robert Meyer[89] suggested that granulosa cell tumors arise from vestigial rests or clusters of superfluous granulosa cells not consumed in the process of follicle formation. Novak[85] accounts for the frequent mixtures of granulosal and thecal tissue in the same tumor by postulating a common progranulosal and prothecal mesenchymal origin. This undifferentiated "mother tissue" is capable of differentiating into either predominantly epithelial (granulosal) or predominantly interstitial (thecal) tissue. Because of their common origin he suggests that granulosal and thecal cell tumors are both subvariants of *feminizing mesenchymoma* of the ovary. Willis[90] and Teilum[91, 9] extend the concept of common origin to include the groups of masculinizing as well as feminizing tumors, the latter worker finding a morphologic and functional congruence goes still further and believes all of these special ovarian tumors to be homologous with certain hormone producing tumors of the testis.

The more widely held theories of histogenesis embrace the concept of embryonal tissue as a progenitor of new growth formation. However, there is no reason for not supposing that normal adult ovarian structures can also be the springboard for neoplasia. This possibility is supported by the experimental production by x ray irradiation of granulosa cell tumors in mice.[98, 111, 11] Similar observations in the rabbit strengthen the hypothesis that granulosa cell tumors in the human may also arise from adult tissues rather than from embryonic rests.[95]

It is not intended to explore the controversial aspects of ovarian tumorigenesis. Recognizing our limitations in this respect, certain pathologic

clinical and hormonal data make it more practical to consider the feminizing tumors as separate entities.

Granulosa Cell Tumors.—These are the most frequent hormone producing ovarian tumors, comprising about 10 per cent of all solid ovarian malignancies.[illegible] They are usually unilateral but bilateral involvement occurs in 5 to 10 per cent of cases.[illegible] They may occur at any age of life, but the majority are found after the menopause. In a review of 62 cases Hodgson and her associates[illegible] *noted an incidence of 60 per cent in the fifth, sixth* and seventh decades with an overall average age of fifty-two years. An infant seventeen months of age with periodic vaginal bleeding is the youngest recorded patient.

Pathologically, there is an extreme variation in the microscopic picture. The anatomic details are not vital to the present discussion and are readily available in the many excellent treatises on the subject.[illegible] For our purposes it is important to know that marked histologic variations do occur and that they account in part for some of the confusion regarding nomenclature and classification. The occurrence of theca cell elements within these tumors is frequent enough to compel some workers[illegible] to *avoid a differentiation between the 2 tumors and to refer to them as the* granulosa-theca cell group. Although "pure" forms are encountered, these are relatively infrequent and the majority consist of mixtures in which one type of tissue or the other predominates.

Apart from the nonspecific clinical manifestations of tumors in general, these neoplasms may produce striking endocrine and systemic effects. This is due to the elaboration of excessive amounts of estrogenic hormone. The influences of hyperestrogenic stimulation are more apparent in the prepuberal child or in the postmenopausal woman. In the adult woman before the menopause the effects are apt to be obscured by estrogenic stimulation which is physiologic at this time. It is to be emphasized that *hormonal effects* are not invariably present, having been absent in 28 per cent of a group of [illegible] patients.[illegible]

The clinical characteristics are most striking in the prepuberal individual where precocious pseudopuberty is produced. This is recognized by the premature appearance of periodic uterine bleeding, enlargement of the uterus, vagina and external genitalia, mammary hypertrophy (occasionally with colostrum secretion) and pubic and axillary hair. This type of precocious maturation is known as pseudopuberty in distinction to true precocious puberty where the adult type of ovarian function appears prematurely. In such instances fertility may be present because of the ability of the ovaries to ovulate and form corpora lutea. This cannot occur in girls with *granulosa cell tumors because the endocrine effects* are due entirely to estrogen hypersecretion and there is no associated follicle function. Because of osteoblastic stimulation the child may grow in height more rapidly than her contemporaries. However, premature closure of the epiphyses of the long bone may result ultimately in a stature which is shorter than average. On the other hand, growth may proceed normally.[illegible]

During the childbearing era the external clinical manifestations are minimal and are distinguished principally by menstrual irregularities. These are similar to those discussed in the previous section in connection

sults in masculinizing effects. Rarely, the ovary develops a hyperfunctioning thyroid tumor of teratomatous origin which causes the clinical manifestations of hyperthyroidism. Lastly, there is a tumor believed to be nonfunctional which is, nevertheless, occasionally accompanied by endocrine disturbances. This is the dysgerminoma. For the present the various endocrine tumors of the ovary may be grouped as follows:

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It is not intended to explore the controversial aspects of ovarian tumor genesis. Recognizing our limitations in this respect, certain pathologic

of mammary carcinoma in association with granulosa cell tumors. In the control group of irradiated mice that did not develop ovarian tumors only a very small percentage developed mammary carcinoma.

Actual assays of hormones have been carried out in a number of cases. The recovery of excessive amounts of estrogenic substance from tumor tissue has been reported by a number of workers.[99,100,105,108,110] Preoperative urinary assays reveal an increased excretion of estrogens[114] with low levels of gonadotropin.[94] The latter observation is consistent with the suppressive effect of large quantities of estrogen on the gonadotropic activity of the adenohypophysis. In no instance has the abnormally present estrogen been isolated or chemically identified. Removal of the estrogen producing tumor results in a prompt decline in the urinary excretion of estrogens[93,94] while the urinary gonadotropins rise to normal or increased levels if the patient is in the postclimacteric era or is castrated.

The malignancy of granulosa cell tumors has been variously estimated and is much less than that of ovarian cancer in general. A clinical malignancy rate judged by recurrences and metastases of 28 per cent was found by Novak and Brawner[101] in their study of 76 cases. On the other hand, Willis[92] points to a relatively low incidence of malignancy in his own and others' series. Hodgson and her coworkers[97] also found a relatively low order of malignancy in their 62 cases. A recurrence of the growth after surgical ablation is often accompanied by a reappearance of the symptoms described above. In 1 reported instance[100] removal of the tumor at the age of forty three years was followed twenty years later by death from widely disseminated metastases.

The treatment of these tumors is always surgical and is followed by a complete regression of the abnormalities induced by the hyperestrogenic state. In 3 cases pregnancy occurred after successful extirpation of the tumor.[93] The decision as to whether a conservative or radical procedure should be performed depends upon the age of the patient and the local operative findings. In younger patients with a well-encapsulated unilateral tumor the uterus and opposite ovary may be left intact. If there is evidence of malignancy a complete bilateral salpingo-oophorectomy and hysterectomy is indicated. This radical procedure is also recommended for patients in the older age group even if the tumor appears small and benign. This is because of the higher incidence of recurrence and associated uterine cancer in woman past middle life. Postoperative radiotherapy has been reported to be of value when the removed tumor is definitely malignant.

Theca Cell Tumors.—These are also known as thecomas and, as previously mentioned, are not universally accepted as a distinctive and specific tumor type. However, it has been pointed out[89,93,104] that there are sufficient clinicopathologic reasons for regarding this tumor as a definite entity.

First described in 1932 by Loeffler and Priesel[106] these tumors have been recognized and reported in increasing numbers. Six cases were added from our hospital in 1938 by Geist and Gaines[103] and 23 from the Mayo Clinic in 1945 by Banner and Dockerty.[104] Statistically this tumor is relatively rare, comprising about 3 per cent of solid ovarian tumors and occurring about one third as frequently as the granulosa cell type. While the average age incidence is approximately the same as that of granulosa cell

with functional uterine bleeding. This is not surprising in view of the hyperestrogenic state which is common to both granulosa cell tumor and persistently functioning Graafian follicles. Uterine bleeding may differ very little from normal menstruation. In most cases, however, it is excessive and irregular and may occur with increased or diminished frequency. In the latter instance amenorrhea occurs and has been noted in about 20 per cent of cases.[93, 94] Because of its tendency to induce uterine bleeding, granulosa cell tumors may cause a resumption of bleeding in patients who are amenorrheic as a result of known extragenital causes. This is exemplified in an acromegalic who lost her menses at the age of forty years and began to bleed again one and one-half years later because of a granulosa cell tumor.[106]

In women past the menopause, uterine bleeding may be resumed. It may be periodic and menstrual-like but is usually irregular. Enlargement of the breasts is said to occur[96] but this is probably infrequent because of the general lack of responsiveness of the secondary sexual characteristics in the advanced years of life.[9]

Evidences of hormonal alterations apply principally to those pertaining to estrogen hypersecretion. In addition to the characteristic clinical signs of hyperestrogenism described above, there are data which reflect the altered hormonal pattern. Most of this is indirect evidence obtained from studies of the endometrium and associated pathologic findings. Evidence of a direct nature derived from actual hormonal assays is very meager.

The effects of excessive estrogenic stimulation are frequently apparent in the endometrium. Regardless of the age of the patient, a proliferative phase is noted in the majority. Less often but quite characteristically, an hyperplastic endometrium of the cystic "swiss cheese" variety is encountered. This is ordinarily indicative of prolonged and excessive estrogenic stimulation although it is well known that an identical endometrial pattern is occasionally encountered in the postmenopausal woman where no estrogen producing lesion can be found. The failure to demonstrate a proliferative or hyperplastic endometrium does not exclude the existence of granulosa cell tumor. In fact, an atrophic endometrium has been noted in instances where the ovarian tumors were small.[93] An interesting finding is the occasional presence of a secretory type of endometrium. This is ordinarily indicative of a progesterone effect and may be related to the frequency with which granulosa cell tumors show partial luteinization.[8, 93]

Inferential evidence of excessive estrogenic influence is also obtained from a study of associated pathologic conditions. The relatively high incidence of uterine fibromyomas, uterine enlargement due to myohypertrophy, adenocarcinoma of the uterus and endometrial polyps may be construed as being due, at least in part, or related to abnormal quantities of estrogenic hormone. The presence of mammary carcinoma in 3 of 62 cases[93] is higher than should be expected in the average population of this age group. Moreover, these 3 lesions developed simultaneously with uterine adenocarcinoma, an observation which strengthens the supposition of estrogen carcinogenesis as a result of granulosa cell tumor. That this is not improbable is suggested by observations on the experimental production of granulosa cell tumors in mice.[98] X-ray irradiation of the ovaries caused a fairly high incidence

theless whenever encountered these tumors should be regarded as potentially malignant

The treatment of this group of tumors is essentially the same as that described for granulosa cell tumors. Operative removal of the involved ovary and homolateral tube results in a complete regression of symptoms. In younger patients the conservative procedure of simple ovariectomy is usually adequate. A more radical operation is recommended for patients in the postmenopausal group. In these patients the relatively high incidence of associated uterine carcinoma dictates the removal of both ovaries along with the uterus.

Luteal Cell Tumors and Luteoma.—Luteinization occurs in a significant number of granulosa and theca cell tumors. This apparently is the counterpart of the lutein transformation of follicular granulosa and theca cells which occurs under normal physiologic conditions in the adult ovary. Since the process of luteinization carries with it the possibility of progesterone secretion, it is not surprising that secretory types of endometrium have been found in some granulosa and theca cell tumors.[illegible] However there is no biologic proof that luteinized tumors actually secrete progesterone.

When all or the greater portion of the tumor is transformed into luteal tissue it is known as a luteoma. It is morphologically indistinguishable from luteomas which have been described in connection with masculinizing tumors of the ovary. The most rational view is that of some workers[illegible] who believe that luteomas having feminizing effects are merely luteinized granulosa cell tumors. Those with virilizing effects are of an entirely different origin being derived either from an adrenal rest or from a stromal cell having both luteal and androgenic properties. The clinical features and treatment of feminizing luteomas are the same as those described above.

Diagnosis of Feminizing Ovarian Tumors.—The presence of such a tumor may be suspected under two sets of circumstances. Evidence of estrogenic stimulation at a time when it is not ordinarily expected, i.e., prepuberally or postmenopausally, points to the possibility of an estrogen producing lesion. During the active sexual period when estrogenic influences are normally operative, evidence of *excessive* estrogenic stimulation is usually not very apparent and diagnosis is difficult.

In the prepuberal girl the premature appearance of characteristic clinical signs of estrogen activity in conjunction with a pelvic tumor makes the diagnosis quite likely.

The adult woman before the menopause may have only a nonspecific type of menstrual irregularity. Serial vaginal smears will usually disclose a constant high percentage of cornified epithelial cells. This is due to the persistently elevated levels of circulating estrogens. Endometrial biopsies on repeated occasions may reveal a persistent proliferative phase or true cystic hyperplasia suggestive of uniformly increased estrogenic stimulation. When these findings are noted in association with an ovarian tumor the latter may be regarded presumptively as feminizing in character. However caution must be exercised in attributing bleeding excesses to ovarian tumors. A recent survey of abnormal bleeding in relation to ovarian tumors

tumors (sixth decade) relatively few cases have been described before the menopause and none as yet, before puberty In this respect this tumor differs sharply from the granulosa cell variety which is known to afflict prepuberal girls It also differs in the fact that involvement is almost always unilateral

Microscopically there are bundles of broad epithelioid appearing spindle or polygonal cells usually showing centrally placed nuclei rich in chromatin The cytoplasm is vacuolated by deposits of doubly refractile fat containing cholesterol and cholesterol esters [103] This is said to distinguish theca cell tumors from the granulosa cell type where the lipoid is located in the extracellular connective tissue [96] The theca cells are separated by extensive bundles of hyalinized connective tissue In some cases this stromal development may be so marked as to create a fibroma like appearance In fact Geist and Spielman[96] suggest that many cases of so called ovarian fibroma or fibrosarcoma associated with changes in sex characteristics which have been reported in the literature may in reality belong to this group of tumors In a significant number of theca cell tumors careful microscopic examination reveals granulosa cells interspersed in the predominant theca cell type [8, 104]

The endocrine effects of theca cell tumors are identical with those produced by tumors of granulosa cell origin since they similarly secrete excessive quantities of estrogen A correlation is said to exist between the presence of hormonal changes and the existence of doubly refractile fat in the theca cells [103] Because the great majority of cases occur after the menopause the outstanding clinical sign is irregular bleeding at a time when the individual should be amenorrheic During the childbearing era there may be menometrorrhagia separated by prolonged intervals of amenorrhea The menstrual irregularities present the same variability as those encountered in patients with granulosa cell tumors As previously mentioned very little if any effect on the secondary sexual characteristics is to be expected in postmenopausal patients

Evidences of hormonal alterations are similar to those which hold for granulosa cell tumors Cystic endometrial proliferation and hyperplasia are noted in a majority of cases Although this is an occasional finding in the nontumor bearing postmenopausal woman its high incidence in the present group of cases points to increased estrogenic stimulation as the cause In a small percentage of cases endometrial atrophy is found [104] The occasional presence of a secretory endometrium[104] suggests that functioning luteinization may occur in these tumors

A frequent association of myometrial hypertrophy uterine fibromyomas and cancer of the uterus has been recorded [104] While there is no proof that the last two lesions are ordinarily due to estrogenic stimulation their increased incidence in these patients is at least suggestive of this possibility under special circumstances

Hormonal assays are very meagre in patients with theca cell tumors An estrogenic substance has been demonstrated in an extract of tumor mass by Geist and Spielman [107] The quantities obtained were larger than those demonstrable in placental tissue

Malignancy in theca cell tumors is of a low order of frequency and tends to be correlated in direct proportion to the degree of cellularity [103] Never-

any one given patient. In certain instances some of the more common manifestations such as amenorrhea and hirsutism may be absent.

Arrhenoblastoma.—This tumor was first described by Pick[114] who found it in the ovotestis of an hermaphrodite and termed it *adenoma tubulare (testiculare ovarii)*. This highly differentiated form of tumor is generally devoid of masculinizing effects and was regarded by Pick as arising from the male constituents of the gonad. Most present-day investigators adhere to Meyer's[117] original concept that the tumors named arrhenoblastoma by him arise from certain misdirected cells. The latter are embryonic rests possessing masculine potentiality which are normally present in the indifferent ambisexual embryonal gonad as the rete ovarii and medullary cords. It is believed that they may persist as vestigial remnants in the normal adult ovary and give rise to tumor formation. It was Meyer who first demonstrated the wide variety of microscopic changes exhibited by these tumors. He also established a relationship between Pick's well differentiated tubular adenoma having a strong resemblance to normal testicular structure, and the less-differentiated forms containing only a semblance of tubule formation and interstitial (Leydig) cells. Geist[56] pointed out that hormonal influences are apt to be in direct proportion to the degree of cytologic dedifferentiation. The more mature cellular structures are generally accompanied by less, if any, androgenic effects.

In general, the histopathologic appearance is characterized by varying grades of similarity to testis structure. Cellular elements may be arranged in adenomatous formation or in cords, columns or tubules. Interstitial cells resembling testicular Leydig cells can often be identified. It is possible that the androgenic secretion may be derived from these cells, although this has never been proven. In its least differentiated or atypical form the tumor presents a sarcomatous appearance. Although the microscopic diagnosis of arrhenoblastoma is fairly easy, the picture is occasionally confused by the presence of typical granulosa cell growth within the tumor structure. This has given rise to the term *gynandroblastoma* for tumors which apparently exert both masculinizing and feminizing effects.[11, 119]

Arrhenoblastomas are relatively rare and are usually unilateral. Iverson[118] recently reviewed 94 cases including 3 of her own. The average age of patients is thirty-two years which is considerably younger than that for the feminizing group of ovarian tumors. However, no patient younger than sixteen years of age has yet been known to develop this tumor. Cases beyond the menopause are not infrequent. Only a small proportion of these tumors are malignant.[56, 6]

Hormonal assays in general show an increase in urinary androgens and neutral 17-ketosteroids and a decrease in estrogens and gonadotropins.[9, 114] Oddly enough, a few masculinizing tumors have been accompanied by increased estrogen excretion.[9]

An unusual hormone effect has been observed where virilization due to an arrhenoblastoma developed during pregnancy.[1, 6] The patient delivered a female pseudohermaphrodite with an enlarged clitoris. The infant had three periods of vaginal bleeding at monthly intervals. In this instance the maternal tumor apparently exerted an androgenizing effect on the accessory genitalia and possibly on the developing gonads. The first va

convincingly demonstrates the fact that it is rarely, if ever, caused by non hormonal ovarian neoplasms [13]

In the postmenopausal patient the reappearance of uterine bleeding is highly *suspicious of neoplasm*. *The presence of persistently cornified vaginal smears* and a proliferative or hyperplastic endometrium suggests hyperestrogenism as a cause of the bleeding. When vaginal smear examination by the Papanicolaou method discloses no evidence of exfoliated cancer cells an estrogen producing ovarian tumor should be suspected even if it cannot be palpated. The diagnosis becomes quite tenable in the event that histologic examination of complete uterine curettings fails to reveal organic disease of the uterus.

Wherever possible assays of urinary estrogens should be performed. Elevations above the levels normally present at the particular age period of the patient confirm the presence of hyperestrogenism. Failure to demonstrate ovarian enlargement does not exclude the possibility of tumor. The latter may not necessarily be large enough to be palpated especially in an obese patient.

Masculinizing Tumors —Ovarian tumors responsible for virilizing effects in women comprise a more heterogeneous and less clearly understood group than is the case with feminizing tumors. The outstanding tumor type is the arrhenoblastoma which possesses well-delineated anatomic characteristics. Its histologic diagnosis can usually be made without equivocation. Recent studies offer convincing evidence of the existence of a second group of virilizing ovarian tumors, the sympathicotropic ("hilus cell") or Leydig cell tumors. The remainder of the masculinizing tumors of the ovary has been the source of considerable speculation regarding classification and derivation. Because of a remarkable resemblance to adrenal cortical and corpus luteum tissue this group includes the so-called adrenal rest tumors, luteomas, masculinovoblastomas and virilizing lipoid cell tumors.

Regardless of histogenetic considerations, these tumors are capable of producing one of the most striking hormonal alterations known to mankind. This is the syndrome of masculinization or virilization and is apparently the result of an excessive production of androgenic hormones. The initial effects are those of defeminization characterized by cessation of menstruation, sterility, loss of general feminine contours and skin texture and atrophy of the breasts. In some cases amenorrhea is preceded by menorrhagia. Masculinizing effects are soon added. The most common finding consists of hypertrichosis which may necessitate regular shaving. Coarse hair appears over the torso and limbs in addition to the face. The pubic hair assumes a typical male distribution. Further evidence of the male type of hair growth may be seen in temporal recession at the hairline. Other manifestations of masculinization include hypertrophy of the clitoris, acneiform eruptions, loss of libido and a masculine habitus and muscular development. The pitch of the voice is lowered and the vocal cords may be normal, congested or hypertrophied [11]. The junction of the laryngeal cartilages (Adam's apple) may become prominent. It is to be emphasized that the tumors under discussion do not invariably produce masculinization. Moreover all the clinical features are usually not demonstrable in

most workers. It is from these adrenal rests that adrenal tumors of the ovary are believed to arise. However, it is well known that although aberrant adrenal tissue has been observed in the broad ligament and ovarian hilum, it is very rare in the ovary itself.[53, 54] In fact, some investigators[90-92] deny its existence in ovarian tissue entirely and accordingly reject the existence of ovarian adrenal-like tumors.

As previously emphasized, the present imperfect state of our knowledge of ovarian tumorigenesis renders it practical to consider clinical aspects in the interpretation of morphologic findings. From a clinicopathologic point of view, therefore, it is expedient to recognize the existence of adrenal or adrenal-like tumors of the ovary.

Adrenal Rest Tumors.—These are said to be highly malignant. However, successful and complete removal of the tumor is followed by regression of the virilizing signs.[96] It is important, of course, to ascertain that the ovarian lesion is not secondary to a primary lesion in one or the other adrenal gland. Differentiation from a masculinizing luteoma is usually beset with considerable difficulty because of the close resemblance between proliferating adrenocortical and luteal cells. Since the existence of a true masculinizing luteoma is very doubtful,[53, 96] the matter of differentiation is apparently not too important.

The urinary excretion of neutral 17-ketosteroids may be moderately increased, as has been recently reported in 1 patient.[127] Cushing's syndrome has also been recorded in association with this type of lesion.[144]

Treatment consists of surgical extirpation, at which time the pelvic organs should be carefully inspected for evidence of extension.[96] Postoperative radiotherapy is recommended where malignancy is known or suspected.

Luteomas.—As previously mentioned, there is a type of luteoma which is apparently derived by more or less complete luteinization of a granulosa cell or theca cell tumor. These are the so-called feminizing luteomas. Even though they are morphologically indistinguishable from the masculinizing variety, their hormonal effects on the patient serve to identify their true origin.[95, 96] When a luteoma is accompanied by feminization, it should be regarded as of granulosa or theca cell tumor origin. In the presence of virilization it is more accurate to consider its origin to be from an adrenal rest or from some as yet unidentified stromal cell capable of luteinization and androgenic function. In the present uncertain state of our knowledge it is questionable whether a true masculinizing luteoma exists as a specific entity.

Regardless of clinicopathologic relationships, this type of tumor should be treated by removal.

Diagnosis of Masculinizing Ovarian Tumors.—The virilizing syndrome produced by these tumors is usually sufficiently characteristic to render its recognition quite simple. However, in instances where amenorrhea or slight hirsutism is the sole endocrine effect, the masculinizing influence of these tumors may escape detection. In this event it is necessary to evaluate local and systemic conditions as well as genetic and constitutional factors. The finding of a solid ovarian tumor, of course, draws attention to the possibility that the clinical manifestations may be due to hormonal influences from this source.

ginal bleeding occurred on the fourth postnatal day and is not a rare event in normal female infants. It presumably represents a withdrawal effect from the previously high levels of circulating estrogens. The second two bleeding episodes cannot be explained but at least suggest that a uterus and vagina were present.

Treatment of arrhenoblastoma is by operative removal. This results in regression of practically all the evidences of virilization although the voice changes may persist. Regular menses may return in one month after operation and this has been followed by pregnancy in some cases.[118] The pattern of urinary hormonal excretion also returns to levels which are normal for individuals of corresponding age.

In younger patients simple ablation of the ovary and tube on the affected side is sufficient. Hysterectomy and removal of the adnexae on both sides are recommended in older women or those past the menopause. The more radical procedure is recommended because of the greater incidence of malignancy in tumors at this age.

Sympathicotropic, Hilus Cell or Leydig Cell Tumors.—In 1923 Berger[1 0] described characteristic cells in the hilum of the normal ovary and the mesovarium which have been called sympathicotropic cells because of their apparent relationship to the sympathetic nerve fibers in this region. On the basis of very suggestive morphologic and histochemical studies these cells are held to be indistinguishable from the Leydig cells of the testis. They are thought by some workers to be the site of androgen elaboration in the normal ovary and to serve as progenitors for the development of certain masculinizing ovarian tumors.[121, 1 1 3] Satisfactory microscopic and histochemical methods have been employed to establish these tumors as an entity distinct from those of adrenal rest or luteal origin. A total of 4 acceptable cases have been reported to date. In each case a well-defined virilizing syndrome was present. Regression of the abnormal endocrine findings was noted after tumor removal in 3 cases (the postoperative developments are not mentioned in the fourth patient). The urinary excretion of 17 ketosteroids was studied in 3 patients. It was normal in 2 and distinctly elevated in 1.[1] The increased excretion dropped to normal after the removal of the tumor. Sternberg[1 3] suggests that some hilus cell tumors may have been misdiagnosed as arrhenoblastomas, adrenal rest tumors or luteomas.

Adrenal Rest Tumors, Luteomas and Others.—These tumors are grouped together because they are the source of considerable confusion and are differentiated from one another only with difficulty. This group also includes "virilizing lipoid cell tumors"[87] and "masculinovoblastoma" of the ovary. The latter is said to originate from adrenal rests[1 4] or from lutein cells.[1 5]

Most of the obstacles which stand in the way of universal agreement have to do with two major considerations. The first is the marked resemblance between adrenal cortical and luteal tissue which often have identical morphologic characteristics. For this reason adrenal rest tumors are difficult to distinguish from luteomas. Secondly is the question as to whether ectopic adrenal tissue ever really gives rise to tumor formation in the ovary. Because of intimate embryonic relationships inclusions of adrenal cortical tissue within the substance of the ovary is accepted by

ovarian strumas are those which contain thyroid tissue exclusively or at least predominantly. In this event all or most of the original teratomatous tissue has been replaced or overgrown by thyroid tissue.

Ovarian strumas are usually unilateral and benign. However, some of these tumors are definitely malignant and have been known to cause death with extensive metastases. Ascites is a frequent accompaniment in the malignant cases. Hyperthyroidism has been reported in both the benign and malignant forms but it is questionable whether the clinical manifestations in the latter were due to actual hyperfunction of the malignant thyroid cells or to the nonspecific effects of a wasting malignant disease.

It is to be emphasized that endocrine effects are not always present in this disease. Moreover, there are no feminizing or masculinizing influences.

Treatment consists of surgical ablation of the involved ovary and its tube. When malignant and operable, panhysterectomy with bilateral salpingo-oophorectomy should be performed.

Disgerminoma. — Although this type of ovarian tumor is not known to produce endocrine effects on its host, it is accompanied by genital disturbances in a sufficient number of cases to warrant its consideration in the general group of tumors under discussion. This tumor was originally called a large round cell carcinoma or "*seminoma*" of the ovary because of its morphologic identity with similar tumors occurring in the testes.[13] It was believed to originate from testicular elements in the ovarian hilum. At the present time the precise origin of these tumors is unknown but the prevailing opinion is that of Meyer.[117] According to this concept the tumor arises from neuter (disgerminal) cells of a sexually undifferentiated type. The presence of these cells in the gonads of both sexes is believed responsible for tumor growth of identical histologic structure in the ovary and testis. It is for this reason that Meyer employed the term disgerminoma[105] (not dysgerminoma) which is derived from *dis*, the Greek prefix for twice, and *germinoma*, gonadal tumor. These primitive germinal cells are not yet tinted with sexual potentialities and hence tumors derived from these cells have neither feminizing or masculinizing effects. In this respect these tumor progenitors differ from those which give rise to feminizing granulosa cell tumors or masculinizing arrhenoblastomas. The origin of such tumors is presumably from precursors which are already differentiated along female or male lines, respectively.

As previously mentioned, this tumor may arise in the gonads of normal women and men. They have also been described in individuals with genital and gonadal developmental defects. These include male and female pseudohermaphroditism, true hermaphroditism, male cryptorchidism, females with defective genitals and young women with poorly developed or hypoplastic ovaries.

Disgerminoma predominantly affects younger women, the majority being under thirty years of age.[90] The reported age range is from six to fifty-two years.[56] Its general incidence is about one third that of granulosa cell tumors.[85] It is frequently malignant although not to the same extent as its counterpart in the testis. The incidence of malignancy is less than that of granulosa cell tumors but more than that of arrhenoblastomas.[56]

In all cases, it is necessary to secure confirmatory data regarding the causal relationship between a palpated tumor and the clinical signs. Unless this is done many needless operations will be performed on women who present slight hirsutism or menstrual irregularities due to other causes. Even in the presence of a well developed virilizing syndrome it is imperative to exclude other etiologic factors, particularly in the pituitary and adrenal glands. Basophilic adenoma of the adenohypophysis is usually accompanied by a combination of metabolic disturbances which are rarely ever found with virilizing ovarian tumors. These include a typical full round moon like facies, a buffalo type of obesity where large accumulations of fat are deposited around the shoulder girdle, osteoporosis, purplish striae of the skin, polycythemia, hyperglycemia, glycosuria and hypertension. Hyperfunction of the adrenal cortex caused by hyperplasia or neoplasm may also cause a masculinizing syndrome. In these cases the urinary excretion of neutral 17-ketosteroids may reach extremely high levels although normal quantities are occasionally found. An increased urinary excretion of 17 ketosteroids is also noted in the presence of certain masculinizing ovarian tumors but only to a moderate degree. The diagnostic differentiation of the various extra-ovarian causes of virilization is discussed in detail in other chapters.

The value of laboratory assays of hormonal function is usually confined to the mere confirmation of the presence of hypoestrogenism and hyperandrogenism without assisting in the localization of the cause. Vaginal smears and endometrial biopsies are usually of the atrophic type indicating a lack of estrogenic stimulation or an excess of androgenic influences. Direct bioassays reveal low urinary estrogens although increased excretion has been noted in a few reported cases. Androgenically active substances are usually present in increased amounts. The excretion of neutral 17 ketosteroids is occasionally increased to a slight or moderate degree. Gonadotropin excretion is usually low due to the suppressive effect of excessive amounts of gonadal hormones on the anterior pituitary.

Abdominal exploration is indicated in the presence of a definite masculinizing syndrome when precise localization of the cause cannot be established. Even when an ovarian tumor has been palpated pre-operatively or is found at operation the incision should be large enough to permit adequate exploration of both adrenal areas with biopsy examination if necessary.

Struma Ovarii.—Thyroid tumors of the ovary are included among the so-called endocrine tumors because they occasionally secrete excessive amounts of thyroid hormone. Under these circumstances functionally active ovarian strumas may produce clinical evidences of hyperthyroidism. Novak[85] cites 5 cases from the literature illustrative of this very rare condition. In 1 case[18] removal of the thyroid-containing ovarian tumor resulted in abatement of the hyperthyroidism.

These tumors are very rare, about 50 having been reported by 1942.[86] Although the origin of thyroid tissue within the substance of the ovary has not been definitely ascertained most workers agree that it is derived from pluripotential teratoma cells. Distinctly teratomatous tumors containing thyroid tissue are well known. However according to Geist [86] true

a study of ten cases of virilizing adrenocortical tumors autopsied at our hospital it was found that the ovaries were invariably of normal or decreased size showing little evidence of follicular activity. Occasional atretic follicles were encountered and recent corpora were absent while corpora albicantia were relatively conspicuous. A review of postmortem material in similar cases reported in the literature corroborated these findings. In general the ovaries were described as small, atrophic and fibrotic with few atretic follicles and old scarred corpora. Similar regressive changes are found in the ovaries of patients with pituitary basophilic adenoma *and virilism*.

The presence of atrophic nonfunctioning ovaries is not surprising in any masculinizing syndrome irrespective of etiology. It is to be expected that excessive androgens, regardless of their origin, may and often do inhibit ovarian function by means of pituitary suppression. This is true of the uninvolved ovary when the other is the site of a masculinizing arrhenoblastoma or adrenal-like tumor.[114] Suppression of function in the opposite ovary even occurs in cases of feminizing ovarian tumors[82, 104] where excessive estrogens react on the adenohypophysis in a similar inhibitory manner.

In none of the above conditions can the ovary be regarded as playing *an important role in the development of a virilizing syndrome* except, of course, when it is the site of a masculinizing tumor. It was not until the aforementioned publication of Geist and Gaines[31] that attention was drawn to the fact that the ovaries may participate very actively in certain virilizing syndromes. They reported two patients studied at our hospital who manifested a masculinizing syndrome which could not be attributed to any demonstrable cause. A very thorough investigation had failed to indicate adrenal or pituitary disease. Because of pelvic findings indicative of ovarian enlargement exploratory laparotomy was performed in each case. The ovaries were found to be uniformly enlarged and on cut section numerous small follicle cysts, 2 to 7 millimeters in diameter, were situated around the periphery. The ovarian medulla appeared hyperplastic and was flecked with yellow spots. Microscopic examination showed an extensive proliferation of the theca cells especially around the atretic follicles but also around the small follicle cysts. Hyperplasia of the theca cells extended from the perifollicular regions well into the parenchymatous substance of the ovary. The majority of the theca cells showed well-defined luteinization accounting for the yellow color noted grossly. In summary, the ovaries of these patients with unexplained virilism showed moderate bilateral enlargement due to a diffuse theca cell hyperplasia in which extensive luteinization *occurred. To this lesion the term "diffuse luteinization" has been applied.*

The bilaterality of the ovarian lesions and their resemblance to experimentally induced luteinization led the authors to believe that the ovarian effects are secondary to some other condition. The possibility of an ill-defined excessive gonadotropic stimulation was considered. Because of the failure of the masculinizing signs to regress after castration, the ovarian lesions were not regarded as a contributory etiologic factor. No hormonal assays *were performed in these patients*.

As a result of these observations a clinical syndrome was established in which virilism of undetermined etiology is associated with ovaries which

The relative youth of these patients and the frequent association of genital defects inclines most workers to the belief that the tumors themselves are of developmental origin. In other words the neoplasm is the result of rather than the cause of some developmental or hormonal effect. This idea is further strengthened by the fact that removal of the tumor results in no alteration of the endocrine status of the individual.

The microscopic picture is quite characteristic and consists of strand-like or alveolar arrangements of large round or polygonal cells of fairly uniform size. These clusters of cells are separated from one another by a partially hyalinized connective tissue framework which is extensively infiltrated with lymphocytes.

Although congenital sexual abnormalities are frequently associated with ovarian dysgerminoma, it is important to realize that these tumors also occur in otherwise normal women. Pregnancies have been reported both before and after the removal of the tumor.[85] Clitoral hypertrophy, when present, is due to the general constitutional condition and not to any hormonal influence from the tumor for it persists after the tumor is removed. A deep masculine type of voice and hirsutism requiring daily shaving are rare concomitants which Novak[5] believes to be due to mild degrees of pseudohermaphroditism.

Not many hormonal studies in these patients have been recorded. Of particular interest is the occasional demonstration of a positive pregnancy test (Aschheim-Zondek, Friedman) in the urine of these patients.[96,130] This indicates the presence of large quantities of urinary gonadotropic hormone, a not uncommon finding in testicular seminoma. Although gonadotropic hormone has been demonstrated in tumor tissue,[56,96] it is not known definitely whether it is formed there or merely stored. The significance of these observations is entirely unexplained at the present time although the possibility of atypical teratomatous elements as a source of chorionic gonadotropin has been suggested.[130] No important deviations in the excretion of estrogens or androgens have been reported.

Treatment of dysgerminoma is surgical removal. In younger patients, especially children, ablation of the tumor-containing ovary and tube is usually sufficient when followed by radiotherapy.[56] However, even when a large tumor is found at operation the apparently uninvolved ovary should be carefully examined in order to detect a small second tumor which might otherwise be overlooked.[96] Hysterectomy with removal of both adnexae is preferable in older women and should be followed by radiotherapy.

Virilization and Nontumorous Ovarian Disease. Syndromes of Diffuse Luteinization and Microcystic Disease.—Exclusive of ovarian neoplastic disease, the role of the ovaries in relation to the masculinizing syndrome received but sporadic and scant attention until it was comprehensively explored by Geist and Gaines[131] in 1942. In order to establish clinicopathologic relationships for a new and previously undescribed clinical syndrome, these workers instituted a systematic investigation of ovarian histology in virilizing lesions of the adrenal cortex. Patients with adrenocortical hyperfunction were selected because of the very strong conviction that this is the common denominator in most, if not all, cases of masculinization that are not due to defeminizing ovarian tumors. From

In addition there were a number of unrelated symptoms consisting of headaches fainting spells and buzzing noises in the head Childhood diseases included measles varicella bronchopneumonia otitis media and scarlet fever all before the age of ten years The patient stated that she weighed 3½ pounds at birth having been born prematurely However at the age of one year, she was distinctly overweight and obesity was marked enough to be recalled during early childhood At thirteen years of age she weighed 175 pounds and at seventeen 230 pounds At present her weight is 250 pounds

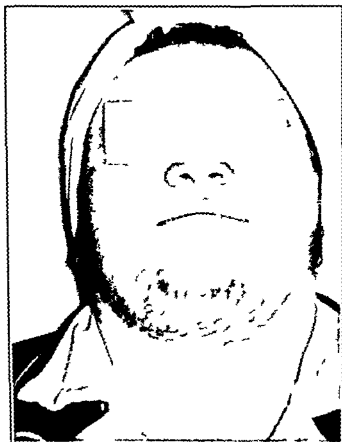


Fig 60 —Diffuse luteinization of the ovaries A 27 year old woman showing marked facial hirsutism and obesity

Although she was markedly overweight there were no other abnormal manifestations when secondary sexual characteristics made their appearance at the usual puberal age The menarche occurred at the age of twelve years with an irregular scanty flow which continued at intervals of two to six months When first examined at the age of seventeen years there was a generalized obesity involving the face limbs and torso There was a considerable development of hair which had recently appeared on the extremities body and face so that she found it necessary to shave every day The distribution of hair in the pubic region was of the male type The clitoris was enlarged to 3 or 4 times its normal size and acneiform lesions were present on the face and thorax

are bilaterally enlarged as a result of theca cell hyperplasia and luteinization That this is a syndrome and not a disease entity is apparent from two lines of evidence Removal of the ovaries does not alter the hormonal effects displayed by the patient Secondly, as Geist and Gaines point out similar ovarian changes were noted by Bergstrand[132] in a patient with a basophilic adenoma of the pituitary and diffuse adrenal hyperplasia In the latter case however, it is not clear that hyperplasia of the stromal cells existed in addition to the perifollicular luteinization which was described [134]

Subsequent reports in the literature[133 134 135 136] have shed additional light on the syndrome under discussion without however adding significantly to our understanding of causative factors or hormonal relationships To date about 8 cases have been reported The clinical features and course of this type of masculinizing syndrome have been accordingly amplified It is now recognized for example that in addition to infertility, amenorrhea hirsutism and clitoral hypertrophy these patients may also have acne a deep masculine voice and small firm breasts In other words a well developed masculinizing syndrome may appear and be as characteristic as that present in association with any of the well known causes of virilism Furthermore, this syndrome apparently occurs only in young women Obesity has been present in two-thirds of the patients Of great importance is the fact that partial ovarian resection is now known to result in varying degrees of regression of the virilizing signs in certain cases This observation was first made by Turner[135] who decided to try partial resection in a patient with this syndrome because of successful results previously reported in sterile amenorrheic patients with bilateral polycystic ovaries [137 138 139] Amenorrhea usually disappears and menstruation may become quite regular Marked hirsutism in an eighteen year old girl almost completely disappeared after removal of a wedge-shaped section from each ovary [135] The clinical improvement noted postoperatively when these patients are treated by partial resection has led some workers to believe that the ovarian lesion plays a primary role [133 135] It has been suggested that large amounts of progesterone produced by the highly luteinized ovarian tissue could conceivably have an androgenic effect Unfortunately there is no direct biologic proof of this theory

The lack of clinical benefit following bilateral ovariectomy may be due in part to the fact that this procedure also removes the potential for estrogenic secretion which is known to exist even in the masculinized state On the other hand in some unexplained manner the procedure of partial resection apparently permits this secretory potential to express itself Although there is no satisfactory explanation for the masculinization in these patients the available evidence certainly suggests that the ovarian lesion itself is at least a contributory factor

The case history of a patient who has been studied at our hospital over a ten year period illustrates many clinical features of this syndrome This case has not been previously reported

A twenty seven year old woman first presented herself at the age of seventeen years complaining of obesity a recent growth of hair on the extremities and face requiring daily shaving and infrequent and scanty menstrual periods

No beneficial results were noted postoperatively. A vaginal smear examination shortly after the operation showed appreciable evidence of estrogenic stimulation while biopsy examination disclosed an hyperplastic endometrium with cystic dilatation of the glands. These findings, not necessarily attributable to the operation, were consistent with two observations. The patient had been menstruating every two to six months and therefore could not have been completely anestrogenic. Secondly, the histologic appearance of the ovaries implied a capacity for secretory function.

Because of the operative failure to induce regression of the virilizing signs, a second operation was performed nine months later with a view to removing a more substantial quantity of ovarian tissue. At operation the right ovary was found to be enlarged to the size of a plum while the left was 1½ times normal size. The major portion of both ovaries was resected leaving only the subcapsular portions. The specimen obtained from the right ovary measured 4.5 × 2.5 × 1.5 cm, while that from the left was the size of a walnut. On section, the ovarian substance had the same appearance as that noted at the first operation. About a dozen tiny serous cysts were also found in the parenchyma, mainly in the cortical region. The microscopic examination again revealed diffuse luteinization of the stroma.

The patient menstruated on the first day after the operation, but it was impossible to ascertain whether this was one of her usual infrequent periods or whether it represented an operative effect. However, the subsequent course demonstrated a distinct effect which could be attributed to the operative procedure. Beginning one month after the operation there was a menstrual flow which recurred approximately monthly for nine months. Thereafter the flow became sparser and occurred at gradually increasing intervals. There was no other demonstrable effect on the clinical course. Further investigations at periodic intervals have failed to elucidate the virilizing mechanism in this patient. Serial vaginal smear examinations show evidence of definite estrogenic stimulation. Another endometrial biopsy disclosed signs of progestational activity. This finding is not uncommon in the presence of extensive ovarian luteinization, although it is by no means pathognomonic. The urinary excretion of 11-oxygenated corticosteroids was normal (1.03 mg. per twenty-four hours). The Friedman "pregnancy test" for increased amounts of urinary chorionic gonadotropic hormone was negative. The twenty-four hour urinary excretion of pituitary gonadotropins was within normal limits.

To recapitulate, this twenty-seven year old woman who had been obese since early childhood developed a masculinizing syndrome some time before the age of seventeen years. Exhaustive clinical and laboratory studies failed to disclose an etiologic factor. The outstanding associated finding was the presence of bilaterally enlarged ovaries. Ovarian enlargement was due to a marked hyperplasia of certain stromal cellular elements which had the characteristic appearance of luteinized theca cells. The morphology of the ovarian lesion was identical with that described by Geist and Gaines[134] as "diffuse luteinization" in the other two patients reported from our hospital. The present patient failed to show appreciable improvement after successive partial ovarian resections were performed. In this respect it was not possible to duplicate a number of successful results reported in the literature.[135, 136]

Turner[135] introduced another descriptive designation for the ovarian histopathology encountered in this clinical syndrome. Acknowledging the distinctive theca cell proliferation and luteinization, this worker is impressed with the numerous small Graafian follicle cysts which usually rim the periphery of the enlarged ovaries. He accordingly prefers the term "microcystic degeneration" of the ovaries. Because the well-developed

During the course of the next six years repeated investigations failed to disclose an etiologic basis for the masculinizing syndrome. Oligomenorrhea gave way to complete amenorrhea and the hypertrichosis continued unabated. Her blood pressure remained within normal limits and urinalyses and hematologic examinations were normal. Also within the physiologic limits of normal were the basal metabolic rate, glucose tolerance test and visual field examinations. No abnormality of the sella turcica could be demonstrated by roentgenographic examination. The kidneys and calyceal structures were well visualized by intravenous pyelography and showed no distortion suggestive of a space-occupying adrenal lesion. No evidence of an adrenal lesion could be demonstrated by roentgen examination after injection of air into the perirenal areas, nor could evidence of adrenocortical hyperfunction be demonstrated by the salt tolerance test.[140] The urinary excretion of neutral 17 ketosteroids was 11.8 mg for twenty four hours, which is normal. The serum sodium was also within normal limits, a result of 135.9 milliequivalents per liter being obtained. The blood chlorides were 562 mg per cent, which is also a normal figure. The serologic test for syphilis was negative. The blood levels for urea nitrogen, sugar, albumin, protein, calcium, inorganic phosphorus and cholesterol were also within normal limits. On purely empiric grounds a course of radiotherapy was administered to the pituitary region. This resulted in no beneficial effects.

When the patient was twenty three years of age surgical exploration and biopsy examination of each adrenal gland was performed with essentially negative findings. Histologic examination merely revealed a prominent zona reticularis on one side and an increased lipoid content of that on the other. Both glands were of normal size. The patient meanwhile continued to manifest the same degree of masculinization which was noted at the first examination six years previously. Scanty uterine bleeding was noted every two to six months. Examination of the pelvic organs had always been unsatisfactory because of the marked obesity. The patient now weighed 250 pounds.

The following year she was readmitted to the hospital because of a ten day history of abdominal pain which was localized to the right lower quadrant. For the first time an adnexal mass was palpated on the right side. For this reason and in view of the inability to demonstrate an extragonadal lesion which might account for her virilizing syndrome, exploratory laparotomy was performed.

At operation the uterus was found to be somewhat hypoplastic and the tubes were normal. Both ovaries were symmetrically enlarged to the size and shape of a hen's egg. They were firm, grayish white on the outer surface and contained many small cystic follicles. Mature or recent corpora lutea were nowhere in evidence. About one-third of each ovary was resected in the shape of a wedge. The cross section showed a markedly thickened medulla containing diffusely scattered small yellow patchy areas.

Microscopic examination of the resected wedges of ovarian tissue showed hyperplasia of the stromal cells which were diffusely luteinized. Where these were especially prominent they accounted for the yellow patches which were noted grossly. Groups of large foamy cells resembling luteinized theca cells were scattered throughout the substance of the ovary. They were round or oval, stained faintly and had small vesicular nuclei. The cytoplasm was finely vacuolated. Irregular strands or accumulations of these luteinized cells were found in both the cortex and the medulla. In many areas these were seen to be contiguous with follicle structures. The majority of atretic follicles showed a well defined zone of perifollicular proliferation of theca cells. Many of these were luteinized and gave the appearance of extending well into the parenchymatous substance of the ovary. Special staining technics showed the luteinized cells to be filled with doubly refractile lipoid bodies. The granulosa cells lining the atretic follicles showed evidence of stimulation. The general appearance of the ovarian stroma indicated that enlargement of the ovaries was due primarily to cellular hyperplasia.

failure of follicle maturation, ovulation and estrogenic function is attributed by Stein[149] to mechanical factors. The thickened ovarian tunica and the crowding of the cortex by the numerous follicles are believed to exert compressive effects. This appears to be *substantiated by the free flow of fluid* under increased pressure observed when the ovaries are incised.

It is thus apparent that there are certain pathologic and clinical resemblances between the syndrome associated with "bilateral polycystic ovaries" and that associated with "diffuse luteinization." The essential differences consist of more striking and constant virilizing signs and obesity and much more marked theca cell hyperplasia and luteinization in the latter. Despite these dissimilarities it is possible that these two clinical syndromes may represent varying degrees of a fundamentally similar endocrine disturbance.

Irrespective of hypothetical considerations, the importance of these studies lies in the fact that otherwise unexplained virilism may be associated with a definitive bilateral ovarian lesion of nontumorous nature. Ovarian enlargement in such cases often cannot be demonstrated by physical examination because of associated obesity. In this event, direct visualization by peritoneoscopy or indirect evidence by roentgen examination of the pelvis after induced pneumoperitoneum[159] may indicate the presence of bilateral ovarian enlargement. If these methods are unavailable or nonrevealing, abdominal exploration may be justified. Even if the ovaries are found to be enlarged, the adrenal areas should also be explored for a possible primary disease. Simple incision of the ovaries will readily disclose the characteristic appearance of diffuse luteinization or polycystic disease and at the same time exclude the presence of a small masculinizing tumor. Bilateral wedge-resection with suture of exposed parenchyma should be performed in the event that diffuse luteinization or polycystic disease is encountered.

A discussion of nontumorous ovarian lesions in association with virilism cannot be closed without drawing attention to a recent report by Sternberg[154]. This worker briefly described 2 women with far advanced virilizing syndromes in whom abdominal exploration revealed the ovaries to be bilaterally enlarged to 8 or 10 times normal size. Except for a single small *follicular* cyst in 1 case, no cysts or follicles were present. Microscopic examination in both cases revealed a significant *hyperplasia of hilus cells*. A great increase in the bulk of the ovarian stroma was present but its significance is not clear. Sternberg adduces considerable evidence suggesting that an increased androgenic secretion by the hyperplastic hilus cells was responsible for the virilizing effects. Further detailed reports of these 2 cases will be awaited with great interest. In the meantime it is well to point out that although these patients were also obese, the approximate age of onset of virilism occurred relatively later in life than in the group of patients described above. Clinical signs appeared at the age of thirty-three years in 1 patient and fifty years in the other. Since this lesion is readily distinguishable grossly from that described as diffuse luteinization or polycystic disease, it poses no immediate practical problem to the surgeon. Complete surgical ablation, possibly with panhysterectomy, seems to be the procedure of choice.

masculinizing syndrome in his patient completely disappeared after resection of two-thirds of each ovary, he regards the ovarian lesion as the primary etiologic factor. As previously mentioned, the weight of evidence and general opinion does not appear to support this contention.

Regardless of etiologic considerations, Turner's therapeutic contribution is a significant one. In the 4 cases previously reported[131-134] bilateral ovariectomy had been performed without amelioration of the arrhenomimetic syndrome. By substituting partial for complete ovarian resection, he was able to induce restoration of regular periodic menstruation, decrease in the size of the clitoris and cessation of hair growth on the face and abdomen. The uterus increased to a normal size and a well-developed proliferative endometrium with some evidence of secretory activity was produced. A recent report from South Africa confirmed the therapeutic effectiveness of partial ovarian resection in 3 patients.[136]

The ovarian lesions which are so characteristic of the syndrome under discussion bear a certain resemblance to those described by Stein and his colleagues[137-139] as "bilateral polycystic ovaries." During the course of a study of women with sterility and amenorrhea these workers found a group of patients having bilaterally enlarged ovaries. At operation, each ovary was enlarged 4 to 5 times and was either elongated or globular. The gonads often presented the appearance of "oyster ovaries" because they were flattened and of an oyster gray color.[137, 138] The capsule was thickened and sclerotic. Upon section of the ovary a clear fluid was released under pressure from numerous small cysts measuring 2 to 15 mm. in diameter. The follicle cysts were usually near the surface but in some instances were found in the hilus. Their number ranged between 20 and 100 in each ovary. Occasionally a larger follicle cyst protruded from the surface in which event the overlying capsule was thin. Corpora lutea and corpus luteum cysts were occasionally present.

Histologic examination of these ovaries is characterized mainly by the presence of numerous follicle cysts. Granulosa layers were present in the lining of all cysts except the very largest. Hyperplasia of the theca layers of the follicles, especially about the numerous atretic follicles, was conspicuous. A well defined luteinization of these proliferated cells was also evident in about one half the cases.

Clinically these patients often showed a tendency toward masculinization. Hirsutism was present in about 50 per cent of the patients and in some cases the growth on the face required frequent shaving. A lowered voice pitch was infrequently noted. Breast development was occasionally reduced. Obesity was present in approximately 10 per cent of the cases. There was no stated attempt to learn whether the virilizing signs, when present, could be correlated with the presence or extent of luteinization.

Outstandingly good therapeutic results following surgical treatment have been reported by these workers and by Robinson.[141] Bilateral wedge-resection with suture of exposed ovarian parenchyma resulted in a resumption of menstruation in 47 of 53 patients treated. Subsequent pregnancy occurred in 20 of these women. The effect on the external evidences of virilism are not clearly evident in the published reports.

No specific etiologic causes have been ascertained. The possibility of congenital, inflammatory or degenerative factors seem unlikely.[139] The

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Chapter 21

THE VIRILIZING SYNDROME

A Summary of the Causes of Virilization in Man and Their Differentiation

The virilizing syndrome is an affliction essentially of females and preadolescent males. If adult males are capable of developing this syndrome it is perhaps beyond the scope of precise clinical recognition, since the concept primarily involves the development of secondary male characteristics of masculinization.

The full blown clinical picture in the female includes hirsutism, amenorrhea, enlargement of the clitoris, a male escutcheon, decrease in the size of the breasts, the development of a bodily male configuration with prominence of musculature, acne, and a change in the character of the voice approximating that of the male due to elongation and thickening of the vocal cords. In adult females there is generally a loss of libido and not infrequently a change in sexual interest from a heterologous to an homologous one. In the young preadolescent male the essential manifestations are the premature development of the secondary male sex characteristics. It is a point subject to argument as to whether the latter actually falls within the scope of the concept of the virilizing syndrome. The tendency has been to set apart precocious sexual development in the young male as distinct from virilization, in part because so many such instances represent constitutional physiologic variations, in part because the puberal age of the male is so variable and ill-defined, and finally because virilism has been accepted as the prerogative of the male of any age. However, since precocious sexual development in the young male is often associated with pathologic states identical with those observed in females with the virilizing syndrome and chemically with an increase in the urinary excretion of androgens beyond what is normally observed for their age, at least this group must be included in the syndrome.

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Chapter 21

THE VIRILIZING SYNDROME

A Summary of the Causes of Virilization in Man and Their Differentiation

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Pathologic Studies.—Sexual development in both normal and abnormal states is determined in the final analysis by the degree of activity of the adrenal and gonad since these glands elaborate androgens and estrogen. Their activity is determined to a considerable extent, however, by other centers, notably the hypothalamus and the adenohypophysis. Although the adrenals and perhaps the gonads are capable of some autonomous activity, the full function of these glands is dependent upon the integrity of the hypothalamic—adenohypophyseal—adrenal pathway and the hypothalamic—adenohypophyseal—gonadal pathway. In addition, the fact that a decrease in size of the gonads and diminution in sexual function so frequently follows primary destructive adrenal cortical disease would suggest that the latter gland also exercise some control over gonadal activity. This effect is perhaps more marked in the fowl and the rat and less so in the human since pregnancies have occurred in patients with Addison's disease. The mechanism of the adrenal gonadal influence is obscure. Some recent clinical and experimental studies would tend to indicate that under certain circumstances at least the adrenals may influence the amount of gonadotropin elaborated by the adenohypophysis. The gonads therefore are true end organs whose activity is influenced by the hypothalamus and the adenohypophysis, with the adrenals perhaps playing some regulatory role. Disease of any of these organs is capable therefore of inducing alterations in sexual function.

The Role of the Hypothalamus in the Development of Sexual Abnormalities.—Bing, Globus and Simon attempted to evaluate the role of the pineal gland and of the mid brain in the production of precocious puberty. They reported on 36 patients under the age of fifteen years, 21 of whom presented pubertas praecox. They emphasized the striking predominance of males in this group since only 1 of the 21 patients was a female. In all instances the lesion of the pineal body had encroached upon or actually invaded other regions of the brain, particularly the mid brain. In 15 of the 21 instances vegetative disturbances associated with hypothalamic disease such as somnolence, obesity, polyuria and polyphagia were noted. Weinberger and Grant[53] pursued this subject further and collected 17 cases of precocious puberty of whom 3 were females. In all 17 instances there was disease of the hypothalamus with no evidence of pineal, ovarian or adrenal pathology. Mid brain tumors were the most common finding associated with this clinical syndrome, although in isolated instances diffuse mid brain inflammatory lesions such as encephalitis, meningo-encephalo-ependymitis, encephalomyelitis following measles, nonspecific inflammations of the brain as well as degenerative encephalopathies were the only abnormalities noted.

It should be emphasized that in addition to the focal neurological disturbances the nature of the sexual abnormalities observed in this entire group of patients with hypothalamic disease was that of true isosexual precocity. The young males exhibited early and excessive facial, axillary and pubic hirsutism, voice changes, somatic growth, enlargement of the genitalia with active libido and spermatogenesis, while the females developed enlargement of the breasts and catamenia.

cortical tumor, the surgical removal of such a tumor is associated with an inordinate operative hazard in the presence of the manifestations of Cushing's syndrome, whereas a similar tumor may generally be removed quite safely where the clinical manifestations are predominantly or exclusively those of virilism,[5] although in several instances complete congenital absence of the contralateral gland in pure virilism has been reported.[63] This difference in surgical risk is due to the fact that in adrenal tumors with Cushing's syndrome, the contralateral adrenal is atrophic and following operation the patient will frequently develop a shock-like state which is often unresponsive to the usual therapeutic measures. This state of shock is unlike that normally observed in Addisonian crisis in that there are no demonstrable disturbances in either electrolyte or carbohydrate metabolism.[61]

In summary, then, our clinical concept of virilism includes the development of secondary male characteristics in young and adult females and in young prepuberal males, with associated pathologic or hormonologic abnormalities not observed in those instances which fall into the group of the so-called physiologic or constitutional variants. The virilizing syndrome may exist purely as such, or may be associated with some or many of the metabolic disturbances characteristic of Cushing's syndrome.

Precocious sexual development in the preadolescent female must be distinguished from the virilizing syndrome occurring in the same age group. The former entity refers to the precocious development of characteristic physical feminine traits. Such children develop enlargement of the breasts, axillary and pubic hair, the latter typically feminine in distribution, and early catamenia. This early isosexual development is in striking contrast to the virilizing syndrome in females in whom the abnormal development is heterosexual in type.

The various types of sexual abnormalities, therefore, may be divided into the following groups:

- A. Prenatal abnormalities
  1. Female pseudohermaphroditism
  2. Male pseudohermaphroditism
- B. In preadolescent females
  1. Precocious puberty or isosexual development
  2. Heterosexual development
- C. In adult females
  - Heterosexual manifestations
- D. Preadolescent males
  1. Precocious puberty or isosexual development
  2. Feminization
- E. Adult males
  1. Possible intensification of masculinization
  2. Feminization

Of these groups, the female pseudohermaphrodite, the young female with heterosexual development, the adult female with heterosexual manifestations, and some forms of precocious puberty in young males fall into the category of the true virilizing syndrome. Adult males with increased virilization constitute an ill-defined and generally unrecognizable group.

tumors are not uncommon in postmortem studies in patients who during life presented no evidences of the disease so commonly associated with adrenal cortical tumors. Similarly in the autopsy studies mentioned above acidophilic tumors of the pituitary were also found. Yet none of these patients showed signs of acromegaly.[33]

The difficulty arises because of the frequent association of bilateral adrenal cortical hyperplasia with pituitary basophilic adenoma. Nevertheless there are authenticated instances of Cushing's syndrome with some virilizing manifestations in whom the only histologic abnormalities noted were pituitary basophilic adenomas.[45]

These briefly noted experimental and clinical studies reveal that pituitary disease is capable of producing minor virilizing manifestations incidental to other more significant abnormalities. Precocious puberty *per se* either iso- or heterosexual however does not occur. Whatever virilizing or metabolic abnormalities are induced are evidently mediated through the adrenal cortex.

The Role of the Adrenals in the Pathogenesis of the Virilizing Syndrome.—The adrenals play a very significant part in the development of the virilizing syndrome. The extent of this influence may be properly appreciated by consideration of the fact that overt adrenal pathology was present in over half of 500 instances of precocious sexual development associated with organic disease collected from the literature.[4,33] To understand the nature of this effect, one must recall the embryologic relationship existing between the adrenal cortex and the gonads. They arise from a common genital ridge and the gonad is then separated from the adrenal cortex which is first specifically noted as such in the 6 mm (4 week) human embryo. Subsequently the adrenal cortex migrates to enclose the neuroectodermal medulla.

The cells of the adrenal cortex secrete both androgens and estrogens. The relation of the various adrenal cortical layers to the secretion of the adrenal steroid fractions has been explored considerably within the last few years. It has become evident that the mitochondrial form may be used as a measure of cell function although perhaps not directly related to the secretory products of the adrenal cortex, while the pattern of the Golgi net is a direct index of the secretory activity of the adrenal cortical cells.[9] Lipid droplets are important in that since the adrenal hormones are lipid soluble ketosteroids they might be expected to be found dissolved in them. There has accordingly been developed a battery of cytochemical tests which are significant in identifying ketosteroids in tissues and hence may be employed in localizing the biologically active hormones of the adrenal cortex. These include the phenylhydrazine, Schiff and semicarbazide reactions which depend on the presence of a ketone or carbonyl group in the reactive molecule; Reichstein's ammoniacal silver reaction in which the carbonyl groups are active enough to reduce ammoniacal silver solutions demonstrates a property exhibited particularly by those adrenal steroids with a carbonyl group at C_{20} and an hydroxyl group at C_{21}. The Liebermann Burchardt reaction which is exhibited particularly by unsaturated steroids, the birefringence phenomenon, and finally the quality of autofluorescence which is manifested

It is evident from these studies that the pineal body plays an incidental role in the production of this syndrome and that what we are dealing with primarily is hypothalamic or mid brain disease the cardinal sexual abnormalities of which are the predominance of male patients and the production of true isosexual precocity. The female patients with this syndrome therefore do not fall within the category of our concept of virilism while the male patients may rightly be included within this group.

The Role of the Adenohypophysis in the Production of Virilism.—Although no pituitary tumor has been known to produce precocious puberty or true virilization as its sole manifestation relatively minor virilizing symptoms have been observed in association with acromegaly. In pituitary basophilism varying degrees of hirsutism and amenorrhea in the female are not infrequently noted. It must be emphasized that this latter disease more prominently is associated with the metabolic abnormalities characteristic of Cushing's syndrome while the evidences of the adrenogenital syndrome are meagre. It is likely that the virilizing manifestations both in acromegaly and pituitary basophilism are mediated through the adrenal cortex.

The question concerning the role that the changes in the basophilic cells of the adenohypophysis characteristic of pituitary basophilism play in the Cushing's syndrome as well as in the occasional virilizing manifestations associated with this disease has been a subject of a good deal of discussion.

The relatively frequent association of the basophil tumors with adrenal cortical hyperplasia raises the perpetual question as to which came first. Experimentally it is entirely clear that the status of the pituitary influences the size of the adrenal cortex considerably. Almost a quarter of a century ago Smith[59,60] demonstrated that experimental hypophysectomy caused atrophy of the adrenal cortex. This of course has been repeatedly confirmed since. Subsequent studies suggested[34] that the adrenal cortical atrophy which followed excision of the adenohypophysis was rather selective in that it was confined particularly to the zona reticularis and the zona fasciculata while the glomerulosa was left relatively intact. With the isolation of the adrenocorticotropic principle[17] from the adenohypophysis it was possible to demonstrate that this fraction produced hypertrophy of the adrenal cortex. There is some further evidence to indicate that this fraction is elaborated by the basophilic cells.[41] Experimentally therefore we recognize the possible role that the basophil cells of the pituitary may play in adrenal cortical function. From the clinical point of view however the significance of tumors of the basophilic cells is less certain. Costello[18] examined the pituitaries of 1000 patients who died of a variety of causes all unrelated to Cushing's syndrome or virilism and basophil adenomas were found in 7.2 per cent. In a similar study conducted by Sussman[67] involving 260 pituitaries 3.1 per cent had basophil adenomas none of which were associated with the classical clinical picture.

These data are really much less impressive than they appear to be at first glance. The fact that such tumors are found in patients who present no signs of Cushing's syndrome does not necessarily minimize their significance. Analagous situations may be pointed to in which adrenal cortical

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The Role of the Adrenals in the Pathogenesis of the Virilizing Syndrome.—The adrenals play a very significant part in the development of the virilizing syndrome. *The extent of this influence may be properly* appreciated by consideration of the fact that overt adrenal pathology was present in over half of 300 instances of precocious sexual development associated with organic disease collected from the literature.[4,35] To understand the nature of this effect, one must recall the embryologic relationship existing between the adrenal cortex and the gonads. They arise from a common genital ridge and the gonad is then separated from the adrenal cortex which is first specifically noted as such in the 6 mm. (4 week) human embryo. Subsequently the adrenal cortex migrates to enclose the neuroectodermal medulla.

The cells of the adrenal cortex secrete both androgens and estrogens. The relation of the various adrenal cortical layers to the secretion of the adrenal steroid fractions has been explored considerably within the last few years. It has become evident that the mitochondrial form may be used as a measure of cell function although perhaps not directly related to the secretory products of the adrenal cortex, while the pattern of the Golgi net is a direct index of the secretory activity of the adrenal cortical cells.[22] Lipid droplets are important in that since the adrenal hormones are lipid soluble ketosteroids they might be expected to be found dissolved in them. There has accordingly been developed a battery of cytochemical tests which are significant in identifying ketosteroids in tissues and hence may be employed in localizing the biologically active hormones of the adrenal cortex. These include the phenylhydrazine, Schiff and semicarbazide reactions which depend on the presence of a ketone or carbonyl group in the reactive molecule. Reichstein's ammoniacal silver reaction in which the *carbonyl groups* are active enough to reduce ammoniacal silver solutions demonstrates a property exhibited particularly by those adrenal steroids with a carbonyl group at C_{20} and an hydroxyl group at C_{21}. The Liebermann-Burchardt reaction which is exhibited particularly by unsaturated steroids, the birefringence phenomenon and finally the quality of autofluorescence which is manifested

by the biologically active adrenocortical steroids, serve to identify the contents of the lipid droplets as ketosteroids. It must be emphasized that no single one of these tests is specific for the presence of ketosteroids but no class of substances other than ketosteroids will react in a positive fashion to this series of tests.[9]

Employing these various criteria, Greep and Deane[9] have demonstrated that hypophysectomy in the rat results in marked atrophy of the zona fasciculata and the zona reticularis while the glomerulosa remains relatively intact and indeed actually broadens. This is associated with histochemical evidence of the disappearance of ketosteroids from the fascicular layer while the lipid content of the glomerulosa remains unaffected. Somewhat earlier Reese and Moon[54] had noted that following the injection of adrenocorticotropic hormone there occurred a striking hypertrophy of the Golgi apparatus particularly in the outer portion of the fascicular layer. The retention of the integrity of the zona glomerulosa following hypophysectomy is significant in that there is a considerable body of evidence which at least suggests the continued secretion of adrenal cortical salt and water-retaining fractions following hypophysectomy.[36,63] On the other hand the relationship of the fascicular layer to the elaboration of the 11-oxygenated corticosteroids is further emphasized by Deane and her coworkers[9] who demonstrated that injections of corticosterone into the intact rat result in alteration in the distribution of the sudanophilic material identical with that observed after hypophysectomy, while the lipids of the glomerulosa remain essentially unaffected. The adrenal response of normal rats to the injection of desoxycorticosterone is in sharp contrast to that which is observed to occur after the injection of the 11-oxysteroids. Following injection of desoxycorticosterone there is a disappearance of lipid from the glomerulosa.[15, 6] Greep and Deane[9] approached this problem in a somewhat different fashion. In the rat twenty-eight days following hypophysectomy, when the lipids of the fascicular layer were greatly depleted and the zona glomerulosa was uninfluenced, the administration of desoxycorticosterone for an additional period of a month resulted in a disappearance of the lipid material in the zona glomerulosa. There is a good deal of difference of opinion concerning the effect of the adenohypophysis on the zona glomerulosa in the human, and at least clinical evidence would indicate that this layer is not entirely impervious to adenohypophyseal influence. Patients with Simmonds' cachexia frequently demonstrate disturbances in electrolyte patterns similar in direction at least to that observed in patients with Addison's disease, while the injection of adrenocorticotropic factor in normal individuals results in at least a temporary decrease in the urinary excretion of sodium, an increase in the urinary excretion of potassium, and hemodilution.[2]

A summary of these studies would tend to show that in the rat at least the zona glomerulosa and the outer layer of the zona fasciculata appear to be most intimately concerned with the elaboration of the adrenocortical ketosteroids. The fascicular layer apparently plays a more significant role in the manufacture of the 11-oxysteroids, these factors having an influence essentially on carbohydrate metabolism, while the zona glomerulosa is apparently important in the manufacture of the salt and water hormone

The origin of the androgenic and the estrogenic fractions in the adrenal cortex is more obscure. The role that the reticularis may play in the secretion of these hormones is *doubtful*. The comparative absence of sudanophilic material containing ketosteroids in this layer would speak against any significant part that it may play in the production of hormones. The lipid material observed in the reticularis contains essentially triglycerides and does not yield positive reactions with the cytochemical tests specific for ketosteroids.

It is generally agreed that in the male animal castration is followed by *adrenal cortical hypertrophy*.[41] *This hypertrophy is due essentially to an increase* in the size of the fasciculate and reticular zones, and such hypertrophy may be inhibited by the administration of male sex hormones.[29] It is of interest that in the human the *X zone* or fetal cortex, which constitutes the larger part of the prenatal adrenal, disappears postnatally, and it is probable that the postnatal reticular zone originates at an early age from persistent cells of the fetal X zone which failed to undergo involution. *In the immature male mouse castration is followed by hypertrophy of the X zone.* However, it must be borne in mind that there is no evidence that the *X zone* of the mouse corresponds to that of the human.

Blackman[8] suggested that the reticular zone of the adrenal cortex is the zone concerned with the manufacture of sex hormones. As evidence of this he presented 9 cases, all ostensibly instances of virilism, in which the zona reticularis was described as increased in diameter and the amount of pigment present in this layer greater than normal. *He concluded that the adrenogenital syndrome* with its associated excessive secretion of sex hormones are phenomena closely related to hyperplasia or tumor of the reticular zone cells. Up to the present time there is no confirmatory evidence of these observations. It would seem, therefore, that the evidence favoring the role of the reticularis in the elaboration of sex hormones is somewhat meagre, and at present no definitive conclusions can be arrived at.

Finally, *Broster and Vines*[10] *have demonstrated a specific staining reaction* with ponceau fuchsin in the cells of the adrenal cortex in 18 cases of virilism, while the *adrenals of normal individuals failed to show this reaction*, nor was it present in tumors unassociated with the virilizing syndrome. The significance and specificity for virilism of this reaction is, however, subject to serious question. Although it was present in 5 instances of virilism with Cushing's syndrome observed at our hospital, it was equally noted in 10 control cases of adrenal adenomas found incidentally at post mortem in patients who during life had no evidence of virilism (48). Cahill and his coworkers[11] found such granules in the adrenals of dogs and in individuals without virilism, although they were present more profusely in cases of *adrenal cortical tumors* with virilism. Sudds[64] demonstrated similar granules in 24 per cent of adult male adrenals and in 28 per cent of female adrenals.

Clinical Aspects of Adrenocortical Hyperfunction.—The clinical manifestations of adrenal cortical hyperfunction are dependent upon the age at which the adrenal pathology develops and the sex of the individual. In a broad sense, the manifestations of adrenal cortical hyperfunction fall into two large categories consisting of (1) sexual and (2) *metabolic abnormalities*.

- A Congenital Adrenal Cortical Hyperfunction
  - 1 Hyperplasia (most common)
    - *a* Early congenital adrenal cortical hyperplasia with female pseudohermaphroditism infrequently with adrenal insufficiency
    - *b* Early congenital adrenal cortical hyperplasia with male pseudohermaphroditism (rare)
    - *c* Late congenital adrenal cortical hyperplasia with adrenal insufficiency
    - *d* Late congenital adrenal hyperplasia with adrenal insufficiency and virilism (uncommon)
- B Prepuberal Adrenal Cortical Hyperfunction
  - 1 Hyperplasia (uncommon)
  - 2 Tumor (generally malignant)
    - *a* In the male
      - 1 Precocious puberty
      - 2 Feminization (extremely rare)
      - 3 Cushing s syndrome with precocious puberty
      - 4 Cushing s syndrome with minor virilizing manifestations
    - *b* In the female
      - 1 Heterosexual precocious puberty
        - *a*) Uncommonly some isosexual manifestations
      - 2 Cushing s syndrome with virilism
      - 3 Cushing s syndrome with minor virilizing manifestations
- C Adult Adrenal Cortical Hyperfunction
  - 1 Hyperplasia (more common) or Tumor
    - *a* In the male
      - 1 Cushing s syndrome with minor feminization
      - 2 Feminization
    - *b* In the female
      - 1 Virilism with or without Cushing s syndrome
      - 2 Cushing s syndrome with minor virilizing manifestations

Pseudohermaphroditism is characterized by the presence of the gonads of only one sex but associated with this are such abnormalities of the external genitalia as to render the identification of the sex doubtful through external examination Male pseudohermaphrodites are those individuals whose gonads are testes while female pseudohermaphrodites have ovaries True hermaphroditism on the other hand is characterized by the gonads of both sexes in the same person The incidence of pseudohermaphroditism is about 0 1 per cent according to Young [88] True hermaphroditism is an exceedingly rare state and to date approximately 40 cases have been culled from the literature [82] True hermaphroditism is an embryologic developmental defect and in contrast at least to many instances of female pseudo hermaphroditism is not related to abnormalities of the adrenal cortex It is interesting that while the relationship between adrenal cortical hyper plasia and female pseudohermaphroditism is well established the cause of male pseudohermaphroditism is still obscure On a purely theoretical basis it is difficult to envision two identical highly specific clinical abnormalities that have not the same common pathologic basis

Male pseudohermaphroditism is 7 times as common as female pseudo hermaphroditism [7] However in at least 15 per cent of female pseudohermaphrodites there is concomitant congenital adrenal hyperplasia whereas this latter state occurs in only 0 7 per cent of male pseudohermaphrodites [27]

Pseudohermaphroditism in the female is essentially a virilizing syndrome This is borne out by the presence of an enlarged clitoris an incom-

pletely separated vagina, the frequent presence of prostatic tissue, hirsutism and a male body configuration. Furthermore, the excretion of the 17-ketosteroids in the urine is markedly increased.

The development of adrenal insufficiency in the female pseudohermaphrodite with congenital adrenal hyperplasia is relatively infrequent, occurring in only 6 out of 58 patients,[4] as contrasted with an incidence of 10 cases of adrenal insufficiency in 16 males with congenital adrenal hyperplasia.

Interestingly enough, the metabolic disturbances of Cushing's syndrome are not observed in the pseudohermaphrodite.

It may be noted, too, that families have been reported with siblings exhibiting female pseudohermaphroditism and male precocious puberty.[8, 17]

Adrenal Cortical Hyperfunction in the Prepuberal Period.—As in all other periods of life, adrenal cortical hyperfunction is more common in *females than in males in the prepuberal period.* During this period, however, the underlying lesion is usually a tumor, and most frequently a malignant one.[8, 14]

In the female, the adrenogenital syndrome is characterized by virilization which infrequently may be accompanied by evidences of isosexual precocity, such as menses or enlargement of the breasts. In no case is tumor associated with pseudohermaphroditism. In the male child, pseudosexual precocity is the rule.

In both male and the female child with an adrenal tumor, the clinical picture observed differs from that seen in hypothalamic disease in that in the latter disorder precocity in the female is always isosexual, and in the male spermatogenesis and enlargement of the testes frequently occurs, phenomena that are but rarely observed in adrenal cortical hyperfunction.[illegible] In the male child, feminization has been reported in one instance.[illegible]

The metabolic abnormalities of Cushing's syndrome are often seen in association with adrenal cortical hyperfunction in the prepuberal group and *generally are associated with mild virilizing manifestations.*

Adrenal Cortical Hyperfunction in Adults.—In the postpuberal group adrenal cortical hyperfunction is more commonly associated with hyperplasia than with tumor. This is in contrast to the preponderance of tumor in the prepuberal group and the universality of hyperplasia in the congenital.

The clinical picture of hormonal secreting adrenal cortical tumors or hyperplasia differs in man and woman. Women afflicted with the disease may manifest predominantly the adrenogenital syndrome, the Cushing's syndrome, or a combination of both. The latter is the most common clinical picture observed. The disease may occur at any age between puberty and the menopause, although most instances are noted between the second and fourth decades of life, with an occasional case occurring after the menopause.[24, 76]

The adrenogenital syndrome in women is characterized by the appearance of male secondary sex characteristics and the suppression of at least many of the female traits. The earliest manifestation is usually the development of hair over the face and extremities and an increase of pubic hair acquiring a male pattern. Coincidental with the appearance of the hypertrichosis, or directly before or after, there occurs an alteration in the menses

They become scanty and infrequent and eventually cease entirely. Associated with this there often occurs a diminution in libido and occasionally even a transfer of sexual interest to other females. There is atrophy of the breasts and a diminution of chest and hip fat. The muscles of the extremities tend to become more pronounced and the entire physical configuration tends to assume the male form. The clitoris may or may not be hypertrophied, the labia are generally dark in color and the uterus and ovaries tend to shrink somewhat in size. The voice deepens and becomes harsh in quality. These manifestations may occur alone but more commonly some or all of these symptoms are associated with evidences of Cushing's syndrome. From the clinical point of view, it is important to bear in mind that the outlook is quite different in those women with an *adrenal cortical tumor in whom the major manifestations are those of* virilism in contrast to those who present in addition the evidences of Cushing's syndrome. As mentioned previously, the removal of the tumor is relatively safe in the former group but associated with considerable hazard in the latter.

Adrenal cortical hyperfunction in the adult male is exceedingly uncom*mon but when it occurs it may assume one or two forms. Either these* patients present a picture of a Cushing's syndrome without virilism or they show actual signs of feminization with very few manifestations of the Cushing counterpart. Even in those instances in which feminization is not predominant there occurs a loss of libido and a decrease in the size of the genitals. The 11 recorded definite cases[60] of the feminizing syndrome in the adult male have two significant observations in common. In all instances the adrenal cortical tumor was malignant in character and none of the patients showed significant evidences of Cushing's syndrome. The feminizing manifestations were enlargement of the breasts and a marked atrophy of the testes. The breasts consisted of loose connective tissue and some true mammary gland tissue. In at least 2 instances a thin milky fluid could actually be expressed from the nipples.[61] In 2 other instances there was a marked increase in the urinary excretion of estrogen and in one a positive Friedman test. More recently an instance of adrenal cortical carcinoma in an adult male was reported in which there occurred a positive *Aschheim Zondek test with a marked increase in the urinary excretion* of gonadotropin but ostensibly no clinical evidences of feminization.

The Role of the Gonads in the Virilizing Syndrome.—The common embryologic origin of the adrenal cortex and the gonads as well as the androgenic and estrogenic potentialities of the gonadal anlage would lead one *a priori* to anticipate syndromes associated with adrenal rests as well as with pathologic development of certain cell types of the gonads.

Adrenal rests may be found in either the ovary or the testis. Nineteen cases with adrenal rests in the ovary have been reported.[38, 53] The presence of adrenal rests in the ovary has been associated with a virilizing syndrome with some manifestations of Cushing's syndrome and it is these metabolic abnormalities that allow a clinical differentiation from the arrhenoblastomas. In the male aberrant adrenal tissue in the testis has been reported in association with precocious puberty[57] and in association with feminization in a twenty-eight year old man.[49]

Leydig cell tumors occur in both the male and female. In the male about 20 cases have been reported, of these 6 were in children.[54] In the prepuberal male pseudosexual precocity ensues while in the adult no sexual alterations generally occur. A few of the cases reported have demonstrated some evidences of feminization. The tumors are usually benign although malignant ones have been described.[50]

In the female 9 cases of either hyperplasia (4 cases) or tumor (5 cases) of the Leydig cell (sympathicotropic cells) of the human ovarian hilus have been reported.[63,51] The clinical picture is that of virilism and removal of the tumor results in cure.

Over 60 cases of arrhenoblastoma have been encountered in the female,[2] but none in a patient under the age of fifteen. They are associated at least in the diffuse type with a virilizing syndrome. The tumors are usually unilateral and are frequently malignant. Their histogenesis is still uncertain. Of interest is the birth of a female pseudohermaphrodite to a woman who developed an arrhenoblastoma and virilism during pregnancy.

Teilum[2] has attempted to simplify the concept of these hormonal tumors of the gonads. He believes that the clinical picture encountered in these tumors can be explained on the basis of homologous tumors (androblastomas) of the ovary and testis derived from a testicular blastoma and differentiating in the direction of Sertoli or Leydig cells. The Sertoli cell tumors secrete estrogen and therefore result in feminization in the male and isosexual precocity in the female. The Leydig cell tumors produce pseudosexual precocity in the male and virilization in the female. He denies the existence of "adrenal rest" tumors and includes them with arrhenoblastomas.

There is another syndrome of the ovary associated with virilization, that of *diffuse luteinization* or *hyperthecosis*.[2,3] It is not clear whether the diffuse luteinization is the cause of the virilization or whether both the luteinization and virilization are secondary effects of the unknown underlying pathogenetic lesion. In favor of the primary role of the luteinization is the fact that subtotal resection of the ovaries may result in a return of the menses.

A group of cases exhibiting bilateral polycystic ovaries with sterility, amenorrhea and virilization has been reported.[64] The genesis of the syndrome is not clear.

Granulosa cell tumors produce isosexual precocity in young females but no heterosexual alteration occurs. It may be noted in passing, however, that the precocious menses are anovulatory.

Constitutional Precocious Puberty.—Constitutional precocious puberty[30,47] is far more common in females than in males. The importance of this condition lies in its differentiation from the pathologic causes of true or pseudosexual precocity. There are no statistics as to the actual incidence of this physiologic syndrome but it undoubtedly is one of the most common of the causes of isosexual precocity. In the male there is enlargement of the genitalia and testes, spermatogenesis as well as skeletal precocity.

Polyostotic Fibrous Dysplasia and Sexual Precocity.—Polyostotic fibrous dysplasia (Albright's syndrome), a disorder characterized by polyostotic

fibrous dysplasia, pigmentation and precocious puberty, is associated with true isosexual precocity in both the female and male, although the incidence of the disease and of precocity is far greater in the female.[120,1]

In the 2 cases examined at postmortem a small mamillary body was noted in 1, and in the other pituitary basophilic hyperplasia, but no hypothalamic lesion was found. It has been suggested that the precocity is due to pressure on the hypothalamus by bony overgrowth at the base of the brain.[1]



Fig. 61.—*Congenital ectodermal dysplasia with hirsutism. 11 month old child.*

It is of interest to note the preponderance of males with precocity in hypothalamic disease as opposed to the preponderance of females observed in constitutional precocity and in Albright's syndrome. In all three disorders, the abnormality is isosexual and represents a true sexual precocity.

In connection with Albright's disease it should be mentioned that several

instances of sexual precocity associated with neurofibromatosis have been reported.[71]

Miscellaneous Diseases Associated with Virilization.—Various other disorders may be associated with virilizing manifestations: 1) teratoma;[66] 2) pregnancy;[illegible] 3) the menopause; and 4) metabolic craniopathy (Stewart-Morgagni-Morel Syndrome).[67] The pathogenetic mechanisms of these are not clearly understood.

It should be noted in passing that Cushing's syndrome with very minor virilizing manifestations has been observed in connection with thymic tumors. In all these instances, a small number, the adrenals were found to be enlarged.[28]

Hirsutism but not Pure Virilization.—Hirsutism in the female is a very common problem and usually no definite factors apart from familial and racial incidence can be indicted as the causative agents. One of the most marked examples of hirsutism may be encountered in congenital ectodermal dysplasia. Although the psychologic needs of the patient often require an intensive search for curable pathologic processes, it is unlikely, in our present state of knowledge, that any more than a small percentage will be found to have one of the syndromes described above.[7]

Some individuals who present hirsutism alone without any other clinical manifestations of virilism have some underlying degree of adrenal cortical hyperfunction as evidenced by the fact that this group will often show a modest increase in the urinary excretion of the 17-ketosteroids. (Fig. 61.)

Hormonal Studies in Virilism.—The adrenal cortex and the gonads are concerned with the elaboration of various androgenic and estrogenic fractions. The sex hormones which have actually been isolated from the adrenal cortex of experimental animals include adrenosterone, 11-hydroxyisoandrosterone, 17-hydroxyprogesterone and estrone.[63] These compounds with the exception of the latter have androgenic activity. Adrenosterone has an androgenic activity equivalent to about 1/5 that of androsterone, 11-hydroxyisoandrosterone about 1/30, while 17-hydroxyprogesterone is about as androgenic as androsterone. The latter compound on oxidation yields Δ_4-androstenedione-3,17 which has even greater androgenic properties and is chemically related to testosterone. It does not, of course, necessarily follow that these hormones are identical with those elaborated by the human adrenal. For obvious technical reasons fractions actually manufactured by the human adrenal would be difficult to isolate and study. However, the degradation products of fractions manufactured by the adrenal cortex and the gonads which are excreted in the urine have been extensively investigated. Comparatively recently Lieberman and Dobriner[64] have isolated 42 different steroid fractions in large collected samples of urine. Of these 15 were α-ketosteroids and 7 were of the β group. Under normal circumstances the ketosteroids commonly found in the urine include androsterone, dehydroisoandrosterone, 3-α-hydroxyetiocholane-17-one, pregnanediol, and estrogens.

In addition to a large number of other 17-ketosteroids not normally present in urine, dehydroisoandrosterone has been found in excessive amounts in the urine of patients with adrenal cortical tumor. $\Delta^{3,5}$-androstadiene-17-one has been isolated from the urine of patients with adrenal

tumor and hyperplasia as well as in some normal individuals. We have identified the presence of this substance in excessive amounts in the urine of a patient with adrenal cortical carcinoma. The urinary excretion of the pregnane-3α-17-20-triols is more commonly associated with adrenal cortical hyperplasia than with tumors, while the pregnane-3α-20-diols are perhaps more often found in tumor although not infrequently seen in hyperplasia. Similarly 3α-hydroxyetiocholane-17-one is excreted in the urine excessively in tumor and only occasionally in hyperplasia.

Adrenal cortical tumors are usually associated with a marked increase in the urinary excretion of neutral 17-ketosteroids. This is true of both benign and malignant tumors. In the latter group particularly, the elevation observed is at least in part due to the marked increase in the β fraction.[40, 1, 7] Under normal circumstances approximately 5 to 15 per cent of the urinary neutral 17-ketosteroids is precipitable with digitonin while in the presence of tumor the proportion may be considerably increased. *In prepuberal virilism due to adrenal cortical hyperplasia,* the urinary excretion of the neutral 17-ketosteroids is elevated although generally not as marked as that observed in tumor. In contrast, adrenal cortical hyperplasia occurring after the onset of puberty is only infrequently associated with an increase in the excretion of the neutral 17-ketosteroids.[14, 31] In both the pre- and post-puberal groups associated with adrenal cortical hyperplasia the proportion of the α to the β fraction is maintained at a normal ratio.[13, 19, 4, 38, 5, 69, 71, 9]

The urinary excretion of the 11-oxysteroids is usually normal in patients with virilization although one such patient with an adrenal cortical carcinoma was reported to excrete a markedly increased amount[60] and high values surprisingly enough have been noted in congenital adrenal hyperplasia with adrenal insufficiency.[56]

In hypothalamic isosexual precocity, Albright's syndrome and in constitutional precocity there occurs a slight increase in the urinary excretion of the 17-ketosteroids for the age group, the levels approximating those observed in normal adults.[37, 46]

In the masculinizing syndromes of the ovary, the excretion of 17-ketosteroids is normal or slightly elevated. In one instance however a value as *high as 54 mgm./twenty-four hours has been reported.*[39, 53]

In the male, interstitial cell tumors may be associated with a marked increase in the excretion of 17-ketosteroids.[78]

Claims have been made for the specificity of pregnane-3α,17,20-triol[10] and pregnanediol[3, 6] in the diagnosis of adrenal virilism.[40] It appears however that although one or both of these compounds may be found in conjunction with virilism due to adrenal hyperplasia or tumor, their presence is not invariable[78, 79] at least in hyperplasia. However, the finding of these compounds may be employed as a confirmatory evidence that the virilism is due to adrenal disease.[40]

Electrolyte and Metabolism Studies in Virilism.—Serum electrolyte abnormalities are not observed in patients with virilism regardless of the site of the basic pathologic process. This is in contrast to what is found in individuals with adrenal cortical hyperfunction manifesting either Cushing's syndrome alone or Cushing's syndrome with virilism. In these latter

groups there is some kind of electrolyte abnormality in somewhat less than half the cases. There may occur an increase in the serum sodium with or without an associated reduction in serum chlorides and potassium or these latter changes may be present alone.

Infrequently there is found a reduction in serum chlorides and potassium and an increase in serum sodium with a marked alkalosis.[illegible]

The Effect of ACTH in Patients with the Virilizing Syndrome.—Lewis and Williams[illegible] compared the effects of ACTH on a patient with Cushing's syndrome and 2 patients with congenital adrenal hyperplasia with virilism. In the patient with Cushing's syndrome the orthodox effects such as an

TABLE [illegible].—CAUSES OF CLINICAL AND TYPES OF SEXUAL ABNORMALITIES

Site of Origin	Age of Onset	Sex	Type of Sexual Abnormality	Pathology	Urinary Excretion of 17-Ketosteroids
Hypothalamus	Prepubertal	Mostly M	Isosexual	Tumor or Inflammatory	N to +
Constitutional Precocity	Prepubertal	Mostly F	Isosexual	Unknown	N to +
Albright Syndrome	Prepubertal	Mostly F	Isosexual	Unknown	N to +
Adenohypophysis	Prepubertal or Adult	M & F	Mixed Virilism with Acromegaly or Cushing's	Tumor Basophil or Acidophil	N to + / N to +
Gonads					
Ovary					
Arrhenoblastoma	Adult	F	Heterosexual	Tumor	N or +
Hilus Cell Disease	Adult	F	Heterosexual	Tumor or Hyperplasia	N
Diffuse Luteinization	Adult	F	Heterosexual	Diffuse Luteinization	N
Granulosa Cell Tumor	Prepubertal	F	Isosexual	Tumor	N
Adrenal Rests	Prepubertal or Adult	F	Heterosexual or Cushing's	Tumor or Hyperplasia	N or +
Testes					
Adrenal Rests	Prepubertal or Adult	M	Precocity	Tumor or Hyperplasia	N or +
Leydig Cell Tumor	Prepubertal or Adult	M	Isosexual	Tumor	N to +++
Adrenal Cortex	Congenital	M	Isosexual Precocity	Hyperplasia	++ to ++++
		F	Pseudohermaphroditism	Hyperplasia	+ to +++
	Prepubertal	M	Isosexual Precocity and/or Cushing's	Tumor or Hyperplasia	+ to ++++ in both
		F	Heterosexual Virilism or Cushing's	Tumor or Hyperplasia	+ to ++++ in both
	Adult	M	Feminization or Cushing's or Both	Tumor or Hyperplasia	N to +++
		F	Virilism and/or Cushing's	Hyperplasia / Tumor	N to ++ / N to +++

N = Normal
+ = Slightly increased
++ = Moderately increased
+++ = Markedly increased

increase in the urinary excretion of the 11-oxysteroids and 17-ketosteroids a retention of sodium and a diuresis of potassium were observed In contrast, in the patients with virilism although there was an increase in the excretion of the 17 ketosteroids there was no increase in the urinary excretion of the neutral reducing lipids In these latter patients, there was a diuresis rather than a retention of sodium

We have studied the effects of ACTH in a patient with Cushing s syndrome and in a patient with virilism associated with diffuse luteinization of the ovaries In the latter instance however, study was undertaken following subtotal resection of the ovaries and subsequent return of her menses although she continued to manifest other evidences of virilism These patients were placed on a careful balance study on the metabolism ward They were injected with 50 mg of ACTH daily in 4 divided doses over a three-day period preceded and followed by similar control periods

In both patients the administration of ACTH resulted in a doubling of the urinary excretion of the 17 ketosteroids and a fivefold increase in the urinary excretion of the 11-oxysteroids In the patient with Cushing s syndrome a retention of sodium but no alteration in potassium excretion ensued In the patient with virilization a diuresis of potassium but no alteration in the urinary excretion of sodium occurred One of the most marked differences observed in the response of the 2 patients was in relation to calcium metabolism In the patient with Cushing s syndrome the injection of ACTH was followed by a marked increase in fecal calcium excretion although the urinary calcium excretion remained essentially unaltered This induction of negative calcium balance is the result of the administration of ACTH in the patient with Cushing s syndrome was in contrast to the lack of effect of ACTH on the fecal and urinary excretion of calcium in the patient with virilism Albright[2] had previously noted an increase in the urinary excretion of calcium following the injection of ACTH

This difference in behavior in these types of patients in terms of calcium metabolism may perhaps be an explanation for the osteoporosis which is so commonly observed in Cushing s syndrome and never seen in pure virilism

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Section IV. The Thyroid

Chapter 22

EMBRYOLOGY, GROSS AND MICROSCOPIC ANATOMY, AND THE PHYSIOLOGY OF THE THYROID GLAND

Embryology of the Thyroid Gland.—The thyroid develops as an entodermal invagination of the floor of the embryonic pharynx between the first and second pharyngeal pouches during the third week of fetal life. This connection between the thyroid and the pharynx, which is the thyroglossal duct, normally disappears when the human embryo reaches the 6 mm. size. Its point of origin persists, however, as a dimple at the root of the tongue and is known as the *foramen caecum*. The invagination from the embryonic pharynx descends to the anterior part of the neck where proliferation of its cells gives rise to the rudimentary thyroid. There was some suspicion that the lateral lobes of the thyroid were contributed to in part, at least, by the ultimobranchial body, but the studies of Kingsbury[1] and Van Dyke[2] render this unlikely, at least in the human.

The rudimentary thyroid consists of epithelial branching plates which really are a solid mass of cells. Connective tissue and blood vessels grow into this mass of tissue, break up the solid cords of cells which increase in number and size and become rearranged to form follicles. This process takes place when the human embryo reaches the 50 mm. size.[3] Colloid appears in the primitive follicles shortly after they are formed, and in the human there is evidence of colloid secretion when the embryo attains a 60 mm. size. It is probable, therefore, that the thyroid assumes functional activity in fairly early embryonic life.[3]

The thyroid gland is present in all true vertebrates beginning with the Amphioxus. Although there are some variations in the gross anatomic structure of this gland in the various species, fundamentally in all species in which the gland is present it consists of follicles containing colloid in which the hormone is stored. Grollman[3] described the gland in the elasmobranch as consisting of a group of follicles which lie at the anterior end of the aorta. In the amphibia the gland consists of a pair of oval bodies which have migrated more cephalad and lie on each side of the lingual bone. In the reptiles the unpaired gland lies over the pericardium, while in birds it is paired and lies in the thorax partially imbedded in the thymus. In mammals it consists of two lobes, one on each side of the trachea, and

in the rabbit, guinea pig, cow, monkey, and man, the lobes are connected by a thin isthmus, which in many other mammals is absorbed during embryonic life.

Gross Anatomy of the Thyroid. — The thyroid gland in the human weighs approximately 20 to 25 grams. When it exceeds 30 grams in weight it becomes just barely palpable on external examination. The gland is situated in the middle third of the neck and is fixed rather firmly to the anterior and lateral parts of the trachea and larynx by fibrous tissue. The isthmus is located just below the level of the cricoid cartilage, lying across the trachea. The lateral lobes of the thyroid are about 5 cm. long and 2 cm. wide, while the isthmus is generally square and measures about 1 × 1 cm. The right lobe of the thyroid is generally somewhat larger and more massive than the left.[4] The *pyramidal lobe* is a tongue-like projection which extends upward from the left side of the isthmus to lie upon the surface of the thyroid cartilage. This lobe is present in most people and is significant in that it becomes considerably increased in size and palpable following thyroidectomy for hyperthyroidism. The thyroid gland is covered with a thin fibrous capsule, strands of which invade the gland proper to produce an irregular and ill-defined lobulation. In addition, the deep cervical fascia separates into an anterior and posterior sheath and encircles the thyroid to form a loose surgical capsule for the lateral lobes of the gland. The ventral surface is further covered by the delicate infrahyoid muscles.

The *parathyroid bodies* are found in close approximation to the thyroid gland. There are four parathyroid bodies, the upper pair of which is generally found close to the posterior aspect of the thyroid gland from the upper pole down to the inferior thyroid vessels. The lower pair of parathyroid bodies is usually, although not always, also found in close proximity to the thyroid capsule on the posterior surface and beneath the lower pole.[4]

The *arterial blood supply* for the thyroid is provided, for the major part, by the superior and inferior thyroid arteries. The former is a branch of the external carotid artery and it spreads over the anterior surface of the upper pole of the lateral lobes. The inferior thyroid artery is a branch of the subclavian artery, and numerous radicles penetrate the posterior capsule of the thyroid lobes at the level of the middle and lower thirds. In addition, smaller vessels, branches derived from the laryngeal, tracheal, and esophageal arteries, supply the medial aspect of the upper poles and the medial aspect of the main body of the lobes.

The *venous return* of the blood from the thyroid gland follows the small arteries to the surface of the gland. The return from the upper pole is by way of the superior pole vein, which follows along the course of the superior thyroid artery and enters the internal jugular vein at about the level of the bifurcation of the common carotid artery. The blood returning from the anterior and middle part of the lateral lobe passes through the lateral thyroid vein directly to the internal jugular. Unlike the superior pole vein which follows along the course of the superior thyroid artery, no major vein follows the course of the inferior thyroid artery.[4] There are two additional systems of venous return, one near the upper pole at the level

of the posterior portion of the insertion of the sternothyroid muscle, and another beneath the sternothyroid muscle both entering the subclavian vein The venous return from the lower pole is to the innominate vein [4]

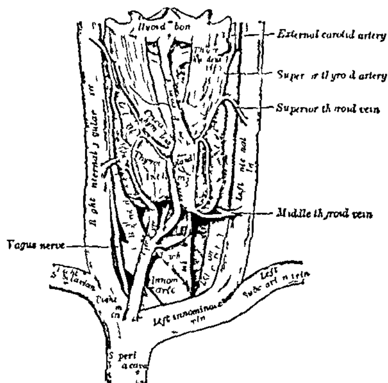


Fig 62 —Dissection of the thyroid body and of the parts in immediate relationship (Gray's Anatomy)

The thyroid gland is rich in lymphatic vessels and the filtering lymph nodes are numerous [5] The *nervous innervation* of the gland is similarly abundant There is a dense network of nerve fibers within and around the follicles These fibers are derived from the pharyngeal branches of the vagus and from the cervical sympathetic ganglion The latter are anterior to the longus colli muscles and somewhat lateral to the thyroid Parasympathetic fibers from the laryngeal nerve also innervate the gland [6] The recurrent laryngeal nerves do not innervate the thyroid but constitute a hazard in surgical procedures on this gland

Histology of the Thyroid —The structural units of the thyroid are the *alveoli* or *follicles* or *acini* These are round oval or irregular sacs which really consist of a closed space lined by a single layer of cuboidal epithelium The average height of the individual cuboidal cell of the normal thyroid is

approximately 15 micra. With increase in thyroid activity the cells tend to become higher in size and columnar in shape. The follicles vary considerably in size and, according to Jackson,[7] may vary anywhere from 30 to 1,294 mu in length in the normal gland. The average follicular length according to this investigator is 163 mu, while Wilson[8] found the average size of the follicle to be somewhat greater. Each follicle is surrounded by a rich network of minute blood vessels and lymphatic channels which is either directly in contact with or close to every alveolar cell.[9] In between the alveoli are lymphoid cells and groups of epithelial cells which appear isolated and unrelated to the follicular structure. According to Rienhoff,[10] however, these apparently interfollicular epithelial cells are by no means isolated cells but represent tangential sections through minute follicles.

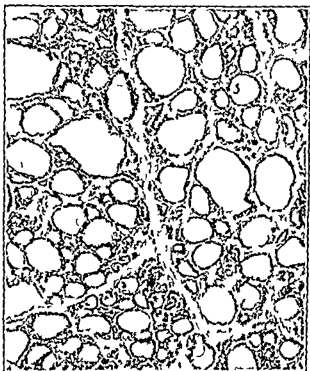


Fig 63—Normal thyroid. (Courtesy of Dr W D Collier.)

The alveoli are filled with *colloid*, which is a protein material, homogeneous, rather viscid and translucent, and acidophilic in its staining properties. The chemical nature of this colloid material is by no means entirely understood. That it is a protein is well established, but whether it is a single protein or a mixture of several has not been determined. Dempsey and Singer[11] have suggested that it is probably a mixture of inert proteins with an active iodine-containing substance. In any event, this protein material is the actual secretion of the gland and contains and stores the active thyroid hormone. The amount of colloid present varies with the

physiologic demands made upon the gland When the activity of the gland is increased the amount of colloid stored is reduced while the antithesis holds when the gland is relatively quiescent

The mechanism of the secretory processes of the thyroid cell is still obscure However at least 3 anatomic factors are probably involved in its secretory activity (1) the thyroid cell itself and within the thyroid cell (2) the mitochondria and (3) the Golgi apparatus The thyroid cell permits its secretion either to pass directly into the perifollicular blood vessels or into the lumen of the follicles where it is stored During the period of increased thyroid activity the thyroid cells increase in height and colloid disappears from the lumen of the alveoli On the other hand when the thyroid activity is reduced the cells flatten out and colloid accumulates within the follicles The direction in which the hormonal secretion passes from the thyroid cell is therefore dependent apparently upon the demand for the hormone When the demand is reduced the hormone is stored in the acini for future use

The *mitochondria* appear in the form of granules rods or filaments and are arranged parallel to the long axis of the cells Goetsch[12] originally described an enormous increase in the number of these forms in the thyroids of patients with hyperthyroidism A decade later Seecof[13,14] studied the mitochondria in experimentally induced thyroid hyperplasia in various animals and found them increased in numbers in hyperplasia and decreased in involution of the thyroid resulting from the administration of iodine Similar studies were reported by Cramer and Ludford[15] at about the same time These investigators found that when increased thyroid activity is produced in the rat and mouse characteristic changes occur in the thyroid cell in relation to the colloid content of the follicles As the cells pass from an inactive to an active phase there occurs an increase in the height of the cell a decrease in the colloid content of the follicle and an increase in the size and number of the mitochondria Uhlenhuth[16] insists that the mitochondria show no changes in response to increased or decreased activity of the thyroid cell as regards hormone production but do respond to alterations in the amount of colloid produced and transported

The *Golgi apparatus* is a reticular structure normally situated near the nucleus of the thyroid cell but which in hyperactive glands becomes more ramified and enlarges into an apical network Porter Claude and Fullam[17] studied the Golgi apparatus by means of the electron microscope and found it to consist of great numbers of droplets or spherical granules fairly equal in size and apparently lipoid in character since they stain intensely with osmic acid stains

With increased activity of the thyroid there occur definite changes in the size structure and location of the Golgi apparatus Williams[9] noted that following the injection of various agents which stimulated the thyroid gland to increased activity there occurred not only an increase in height of the thyroid epithelium an increase in the number of vacuoles present in the colloid and a diminution in the amount of colloid but also a marked hypertrophy of the Golgi apparatus In the presence of decreased thyroid activity colloid reappears and accumulates in the follicles the thyroid cells flatten out and the Golgi apparatus becomes reduced in size

and assumes its position near the base of the cell. Okkels[18,19,20] found that the Golgi apparatus was hypertrophied and extensively ramified in the glands of patients with toxic goiter. This investigator further described certain changes following the injection of thyrotropic hormone into the guinea pig. Within twenty to thirty minutes after the injection definite changes could be observed in the thyroid gland. The cells become swollen and decolorized, the Golgi apparatus disappears, the cell borders remain intact and indeed a distinct limiting membrane is present around that portion of the cell bordering on the follicular lumen. At this stage the colloid in the follicle is still clear and non vacuolated. Within an hour after the injection of thyrotropic hormone fine strands of Golgi apparatus begin to reappear, the limiting cell membrane previously described becomes obliterated and the colloid becomes vacuolated. Within two hours after the injection the follicles become decreased in size, the colloid disappears, and the Golgi apparatus becomes greatly hypertrophied.

The evidence thus far available would indicate that both the mitochondria and the Golgi apparatus within the thyroid cell change in response to altered activity of the thyroid gland. This still leaves obscure, however, the question of whether these elements are specifically concerned with the actual secretion of the thyroid hormone. Worley,[21] writing of the Golgi apparatus in general, suggests that it is directly responsible for the formation of all secretory granules.

The Secretion of the Thyroid Hormone.—Iodine is intimately involved in the formation and secretion of the thyroid hormone. With the advent of radioactive isotopes of iodine[22,23] the investigator was provided with a tool which enabled him to explore more precisely the metabolic activities of iodine and the relation of the thyroid gland to the metabolism of this ion. Hertz, Roberts and Evans[24] and Hamilton[25] made contributions of fundamental importance in the early pioneer work in this field.

Approximately 14 radioactive isotopes of iodine have been identified, but only 4 of these have been used in biologic study.[6] These are

I_{128}	with a half life of	25 minutes
I_{130}		12.6 hours
I_{131}		8 days
I_{126}		13 days

Of these I_{131} is now used almost universally since it is most readily available and its half life is long enough to permit adequate and controlled use. I_{131} is prepared by the bombardment of tellurium with neutrons in the chain reacting pile. This iodine isotope disintegrates into *xenon* and during this process of disintegration each atom of radioactive iodine emits a beta particle and two gamma radiations. The maximal energy of each beta particle is 0.595 MEV (million electron volts) and of each gamma ray 0.360 MEV.[6] Experimental evidence demonstrates that the physiologic and chemical activity of the radioactive iodine isotopes is exactly like that of stable iodine I_{127}, except that the former exercises in addition radiation effects. This applies essentially to all radioactive isotopes.[7,8] It is this fact which permits us to use I_{131} for the study of iodine in relation to thyroid physiology.

Because radioactive iodine emits radiations, we can follow and study its course through the body by picking up these radiations by means of a Geiger counter. Thus, it was found that when radioactive iodine is ingested orally, it is rapidly absorbed from the stomach and can be detected in the human hand within three to six minutes.[4-6] Further absorption from the gastrointestinal tract is three quarters complete within an hour and almost entirely complete within three hours.[5] Only a small amount, approximately 3 to 11 per cent, of the radioactive iodine is excreted in the stool.[29,30] About 10 to 15 per cent of an administered dose of radioactive iodine is not accounted for by thyroid collection or urine and stool excretion.[5] Most of this 10 to 15 per cent fraction is taken up by the various organs, particularly the liver and small intestine, as well as the ovaries, pituitary, lungs, and kidneys.[31,32] A small fraction is lost through exhalation in expired air and by secretion in sweat and in the salivary glands.

The major fraction of ingested radioactive iodine is excreted in the urine within forty-eight hours and only minute amounts after that.[4,28] The rate of disappearance of radioactive iodine from the circulation is at least in part dependent on the degree of functional activity of the thyroid. Thus, as Kelsey, Haines and Keating[4] have shown in normal human volunteers, approximately 11 per cent of the ingested dose disappears from the circulation within one hour in contrast to 30 per cent in exophthalmic goiter and 6 per cent in myxedema. In these same normal volunteers 65 per cent of the total ingested dose is eventually excreted in the urine in contrast to 23 per cent in exophthalmic goiter and 85 per cent in myxedema. This alteration in the degree of renal excretion has little to do with the *rate* of urinary excretion, as is evidenced by the fact that 5.5 *per cent of the ingested dose is excreted in the urine per hour in hyper*thyroidism as compared to 5.4 per cent in myxedema. The difference in behavior is dependent for the most part on the avidity of the thyroid for iodine. However, where there is impairment of renal function there may occur a decrease in the amount excreted in the urine over a given period of time. When this occurs it is not associated with an increase in the uptake of radioactive iodine by the thyroid but rather with an increase in the excretion in the sweat, salivary glands, and exhaled air, and a longer stay in the circulation.

The Utilization of Iodine by the Thyroid.—The metabolism of iodine by the thyroid gland really consists of three processes, according to Vanderlaan and Vanderlaan.[24] The first is concerned with the *accumulation* of iodine by the gland, the second with the *synthesis* of the *hormone*, and the third with the *secretion* of the *hormone* and its discharge into the general circulation. The *accumulation* of iodine by the gland consists of two phases:[6] the *trapping* of inorganic iodide and its conversion to organically bound iodine, and the storage of the latter. By trapping is meant the rapid concentration of large amounts of circulating inorganic iodide, probably in the cells of the thyroid follicles. As soon as iodine or radioactive iodine enters the blood stream, the thyroid begins to collect it and the kidneys to excrete it.[3] According to Hamilton,[35] the thyroid has the capacity to concentrate iodine to 10,000 times the blood level. Present evidence would indicate that only iodides free from protein linkage are selectively collected

by the thyroid, the *rate of uptake being 2 to 4 per cent per hour of the total* iodide present in the blood and body fluids.[35-37] Inorganic iodide is no sooner trapped than it is being converted into organically bound iodine. This latter process occurs in the cells of the follicles and involves the iodination of tyrosine. This phenomenon actually occurs within the protein *molecule and the subsequent condensation of two molecules of diiodotyrosine* results in the formation of *thyroxine*. Both the diiodotyrosine and the thyroxine share in the formation of the protein molecule, *thyroglobulin*, which is then stored in the colloid of the follicle.

The release of the thyroid hormone from the thyroglobulin is probably *due to the presence of a proteolytic enzyme system.*[38] *DeRobertis*[38] *demon*strated the presence of such an enzyme system in the colloid of the thyroid follicles and suggested that it transformed thyroglobulin into smaller molecules which then enabled it to diffuse through the thyroid cells and enter the circulation. The nature of these smaller molecules is uncertain, but *the recent finding of free thyroxine in the blood by two independent* groups of investigators[39,40] at least suggests the possibility that the breakdown of thyroglobulin by the proteolytic enzyme in the colloid results in the formation of thyroxine. Certainly the administration of iodine results in the presence of diiodotyrosine and thyroxine in the circulation. As early as 1941 *Perlman, Chaikoff and Morton*[10] *found that within two hours* after the intraperitoneal injection of radioiodine into guinea pigs newly formed radioactive diiodotyrosine and thyroxine appeared in the plasma. It is possible, therefore, that thyroxine is the actual circulating thyroid hormone, as pointed out by Harington.[41] It has been suggested that thyroxine is *not present as such in the thyroid gland*. *Leblond and Gross*,[4] however, employing the method of isotope dilution, have demonstrated, if not entirely conclusively, at least suggestively, that free radioactive thyroxine was present in thyroid tissue as well as in the plasma. These latter investigators further found that the concentration of thyroxine in the thyroid tissue was approximately 23 times as great as its concentration in the plasma. This difference in concentration they suggest represents a gradient sufficient to permit diffusion of this hormone from the gland *into the circulation*. Leblond and Gross conclude that "thyroxine is in fact the *form in which the thyroid hormone is released by the thyroid and circu*lates in the body."

If the inorganic iodide trapped by the thyroid cannot be utilized for hormone synthesis, most of it passes out of the gland within twenty-four hours and is excreted in the urine.[6] In general, more than 90 per cent of the inorganic iodide trapped in the gland is converted into the organically bound forms within forty-eight hours. In the thyroid itself at any given time 10 per cent or less of the iodine is in the form of inorganic iodide, 25 per cent as thyroxine and approximately 65 per cent as diiodotyrosine which probably is the precursor of thyroxine.[6] The conversion of the inorganic iodide into the organic forms occurs rapidly and begins as soon as the iodide is collected from the circulation. Thus in the dog at least within half an hour after ingestion *8 to 10 per cent of the radioactive iodine* had already been converted to diiodotyrosine, while the thyroxine fraction was 0.3 to 0.4 per cent. Within forty-eight hours almost half of the

ingested dose of radioactive iodine had been converted into diiodotyrosine and the thyroxine fraction was now 2.4 per cent.[43] In the rat the conversion is perhaps even more rapid since 1.5 to 3.0 per cent of injected radioiodine was present as radiothyroxine within two hours after administration.[44]

There is some evidence to indicate that in the rat at least diiodotyrosine and thyroxine are capable of being formed outside the thyroid gland. Thus in the totally thyroidectomized rat ninety-six hours after injection of radioactive iodine 30 per cent of the I^{131} contained in the liver and small intestine was organically bound, 20 per cent as diiodotyrosine and 10 per cent as thyroxine.[45]

The collection of inorganic iodide by the thyroid is a process which is essentially independent of that of conversion and storage of the organically bound iodine although both processes go on almost simultaneously. This independence is shown by the fact that when the synthesis of thyroid hormone is blocked by drugs such as propylthiouracil the thyroid gland is still capable of trapping inorganic iodides following the injection of potassium iodide. The iodide under these experiments is held in the inorganic form and eventually excreted in the urine. The antithesis of this is also true. Thiocyanate, which inhibits the uptake of inorganic iodine, will nevertheless permit the continued conversion of the already trapped iodide to organically bound iodine.

Factors Influencing the Metabolism of Stable and Radioactive Iodine by the Thyroid. — The factors which influence the uptake of radioactive iodine and by that we mean those factors which influence the uptake of iodine fall essentially into two categories: (1) Those factors which determine or influence the degree of activity of the thyroid cells. In this category are included those states or agents which stimulate or inhibit the secretion of thyrotropic hormone by the adenohypophysis. (2) Agents which prevent the uptake or organic binding of iodine by the thyroid.

The action of pituitary thyrotropic hormone in various laboratory animals has been studied in considerable detail. It is now clear that the parenteral administration of this hormone results in hypertrophy and hyperplasia of the thyroid in which the cells increase in size and number. Associated with these histologic changes there is an increase in the uptake by the gland of inorganic iodide, a decrease in the thyroid content of protein bound iodine and an increase in the serum concentration of protein bound iodine. It is obvious that under the stimulating influence of thyrotropic hormone inorganic iodide, be it radioactive or stable, is rapidly taken up by the thyroid, bound to protein, the thyroid hormone is secreted into the follicle, proteolyzed and the hormone discharged into the circulation. According to Leblond and Gross[47] all these processes occur practically simultaneously. The duration of the interval between the injection of the hormone and the increase in the uptake of radioactive iodine apparently varies with the species. Keating and his coworkers[48,49] working with chicks found that daily injections of thyrotropic hormone resulted in an increase in follicle cell height within twenty four hours but an increase in iodine uptake was not manifested until forty-eight hours after injection of the hormone. This is somewhat different from the behavior observed in

humans. Stanley and Astwood[50] injected a single dose of 15 or 30 mgm of thyrotropin in 23 normal subjects and found that for the first eight hours no effect on the uptake of iodine by the thyroid could be detected but thereafter a marked acceleration reaching a peak within twenty four to forty-eight hours, could be observed. The total duration of effect of this single injection was approximately four to five days. Since hypertrophy of the thyroid cell occurs before the first detectable increase in the uptake of inorganic iodide the former apparently is essential for the latter. This accounts for the rather long latent period which follows the injection of thyrotropic hormone before increased thyroid function is manifested.

Stanley and Astwood[50] report that as far as they could determine the increased organic binding of iodine was first detected at approximately the same time that an increase in the uptake of inorganic iodide was noted. Both processes are apparently therefore stimulated simultaneously although relatively independently. This point was demonstrated by the fact that following the administration of mercaptoimidazole, an antithyroid drug of the thiouracil type, the injection of thyrotropin resulted in an increase in the uptake of iodine but no increase in the formation of organically bound iodine.[50]

Factors which influence the amount of thyrotropic hormone being secreted will therefore affect the uptake of iodine by the thyroid. Cortell and Rawson[51] showed that exogenous thyroxine will reduce the amount of thyrotropic factor available to the thyroid. Similarly, the daily administration of relatively large amounts of dessicated thyroid extract to normal human subjects results in an almost complete suppression of iodine uptake. That this is due to the suppression of thyrotropin secretion is evidenced by the fact that the parenteral administration of thyrotropin during thyroid extract therapy again enables the thyroid to take up radioactive iodine.[50] Exposure to stress of one kind or another will cause an increase in the secretion of thyrotropin. Wes[52] found that the injection of epinephrine in the bilaterally adrenalectomized rat caused an increase in the thyroid uptake of radioactive iodine. This increase could be inhibited by the simultaneous administration of 17 hydroxy-11 dehydrocorticosterone (Compound E of Kendall) or by the administration of ACTH.

The influence of the *antithyroid* drugs like thiouracil, propyl and methyl thiouracil, *etc* on the metabolism of iodine is along a different direction. Rawson and his coworkers[53] found that the thyroids of patients with hyperthyroidism given thiouracil prior to subtotal thyroidectomy collected little radioactive iodine. This clinical observation was amply confirmed in the experimental animal.[54, 55, 56] The nature of the effect of these antithyroid drugs is to inhibit the conversion of inorganic iodide to the organically bound form. Studies of thyroid slices in thiouracil baths show a perfectly normal uptake of iodine but a failure of conversion to diiodotyrosine and thyroxine.[57, 58] Further *in vivo* studies revealed that the antithyroid compounds did not interfere with the trapping of inorganic iodide by the thyroid although they blocked the synthesis of organically bound iodine.[59, 60] Because of the failure of the conversion of *inorganic iodide to* the organic form, the former is rapidly discharged from the thyroid and excreted in the urine. Thus the amount of radioactive iodine actually

collected and held in the thyroids of thiouracil treated patients or experimental animals is considerably reduced It is for this reason incidentally that radioactive iodine is not administered to patients either during or directly after treatment with thiourea compounds

The nature of the effect of *thiocyanates* on the metabolism of iodine by the thyroid is still somewhat obscure and contradictory Apparently the *effect of thiocyanates on this function is dependent to some extent upon* whether the drug is administered acutely over a short period of time or whether treatment is more prolonged The administration of a single dose *of thiocyanate inhibits the uptake of iodine and* suppresses its conversion to diiodotyrosine and thyroxine[56,57] Rawson and McArthur[61] reported that the uptake of radioactive iodine by the thyroids of chicks and rats was considerably decreased for a period of one to six hours after a single dose of thiocyanate, but that this defect disappeared after twelve hours These observations were confirmed by McGinty and his group[62] Even when the thyroid gland is completely depleted of organically bound iodine the administration of thiocyanate for short periods of time will inhibit the *uptake of inorganic iodide*[63] *Rawson Hertz, and Means*[64] studied the uptake of radioactive iodine in a patient who had a large goiter caused by the prolonged administration of potassium thiocyanate for the treatment of *hypertension* These studies were conducted while the patient was still being treated with the thiocyanate, and the investigators found a considerable increase in the uptake of the radioactive isotope In the experimental animal notably the rat Rawson and his group[65] found that the total uptake of radioactive iodine by the thyroid following the prolonged *administration of potassium thiocyanate was no greater than that of the un*treated controls and per milligram of thyroid tissue was indeed somewhat less It is at least likely, therefore that the increased uptake in the patient reported above may be more apparent than real It is possible however that there is a marked difference in species behavior The prolonged administration of potassium thiocyanate in the chick does result in an actual increase per milligram of thyroid tissue in the uptake of radioactive iodine[65] Wolff and his coworkers[66] found that in rats treated with potassium thiocyanate the *uptake of radioactive iodine is diminished* as *long as the blood* concentration of thiocyanate is maintained at a high level When the thiocyanate is no longer demonstrable in the circulation the uptake and concentration of the isotope in the thyroid is considerably increased Kelsey Haines and Keating[5] observed similar results in humans with thiocyanate goiters *Although the behavior of these patients in respect to the uptake* of iodine was variable these investigators do report that at least in some instances there was a low uptake when the blood thiocyanate level was high followed by a normal or by a high uptake of radioactive iodine *shortly* after the thiocyanate had disappeared from the blood

The *influence of thiocyanate on the* metabolism of iodine by the thyroid is important because of the wide distribution of this ion Thiocyanate ion normally occurs in the blood and saliva It is present in readily demonstrable concentration in various plants particularly *in the Brassica family* Finally substances such as mustard oils organic nitriles isothiocyanates and cyanogenetic glucosides which are widely distributed in nature, are

readily converted into thiocyanates by the mammalian organism.[78] Astwood[75] suggests that the consumption of large quantities of foods containing these substances may render diets which presumably contain adequate amounts of iodine into iodine-deficient ones.

Hertz and his coworkers[67,68,69] demonstrated that the administration of stable iodine, I_{127}, prior to treatment with radioactive iodine caused a diminution in the uptake of the latter. This is true both for the experimental animal and for patients with Graves' disease. The antithesis of this is also true. Iodine deficient diets are associated with an increase in the uptake of radioactive iodine.[70] Morton, Chaikoff and Rosenfeld[71] studied the metabolism of thyroid slices in various concentrations of non-radioactive iodine, I_{127}, and found that the ability of the thyroid tissue to convert iodine into diiodotyrosine and thyroxine was inhibited when the I_{127} concentration of the surrounding medium exceeded 20 micrograms. Wolff and Chaikoff[2,3,74] subsequently demonstrated a similar phenomenon in *in vivo* studies in the rat. They reported that the thyroid was incapable of converting trapped inorganic iodide to the organically bound form when the serum concentration of iodine exceeded 30 micrograms per cent. A possible explanation for the phenomenon observed in the *in vivo* studies is provided by the observations of our group[5] who found that the administration of iodine to patients with Graves' disease prevented the access of thyrotropin to the thyroid. This results in the histologic changes in the thyroid usually noted in the lugolized patient and a decrease in both uptake of iodine and its conversion into the organic form.

Finally, both thyroxine and thyroid extract will cause a decrease in the uptake of radioactive iodine.[6,77] This effect is probably mediated through two channels: the iodine content of the thyroid hormone prevents the access of the thyrotropic factor to the thyroid, while the thyroid hormone *per se* partially inhibits the secretion of thyrotropin by the adenohypophysis.

The Iodine Content of the Thyroid Gland and of the Blood. — The total iodine content of the body is about 50 mgm. Of this amount the human thyroid contains approximately 10 to 15 mgm, or 0.5 to 1.0 mgm per gram of fresh tissue.[2] Iodine is present in the blood in two forms: (1) as inorganic iodine and (2) as "protein bound" or precipitable iodine.[9,80] The latter fraction constitutes by far the major iodine fraction of the serum. The values in normal individuals for "serum precipitable" or "protein bound" iodine vary from 4.0 to 8.0 micrograms per cent (gamma per cent). The total serum iodine, that is the serum precipitable iodine plus the inorganic iodine, averages 1.0 to 1.5 micrograms per cent higher. The value for the serum inorganic iodine fraction fluctuates considerably depending upon the intake of iodine, while the protein bound iodine remains relatively constant. It is because of its relative constancy that the protein bound iodine fraction is usually used as an index of thyroid activity.

Riggs and his coworkers[80] and Salter[79] have definitely demonstrated that there is an increase in the serum precipitable fraction in hyperthyroidism. This observation has been amply confirmed and in this illness values above 8.0 micrograms per cent are almost always encountered. In the absence of a definite elevation of this fraction the diagnosis of hyperthyroidism must be seriously questioned. In hypothyroidism values are

usually below 10 micrograms per cent. The exogenous administration of inorganic iodine will raise the serum total iodine value by elevating the inorganic iodine level but will not affect the protein bound fraction value. However, the latter is increased following the administration of organic iodine compounds such as are used in radiography, particularly in visualization of the gall bladder and kidneys. The elevation of the serum precipitable iodine which follows intravenous pyelography is rapidly dissipated, usually within a few days, but an elevation of this fraction may persist for many weeks following ingestion of organic iodine dyes for visualization of the gall bladder.

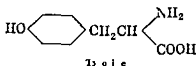
The fraction of the protein with which the organic iodine is associated is not entirely clear. Salter[81] suggests that the major portion of the organically bound iodine in the serum is incorporated in the albumin fraction although lesser concentrations have been found in association with the alpha and beta globulin fractions. In addition free thyroxine is in all probability also present. Inorganic iodide is present equally in both plasma and red cells,[82,83] but there is still a considerable difference of opinion as to whether there is any protein bound iodine in red cells. Silver[84] has failed to find any organic iodine in these cells while McClendon and Foster[85] describe a concentration in the red cells approximately equal to that of plasma. More recent studies would tend to support Silver's contention.

The average diet contains approximately 100 micrograms of inorganic iodine per day[86] and normal individuals generally show a positive iodine balance since the total daily excretion is approximately 42 micrograms.[3] Patients with hyperthyroidism, by contrast, are usually in negative iodine balance since they excrete 2 or 3 times as much inorganic iodine as do normal individuals.[87]

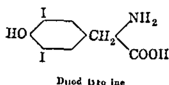
THE CHEMISTRY AND BIOLOGIC ACTIVITY OF THE THYROID HORMONE

The Physiologic Function of the Thyroid Gland.—In 1915 Kendall isolated thyroxine in crystalline form from the thyroid gland and approximately a decade later in 1927 Harington and Barger[89] succeeded in synthesizing this hormone. The synthetic product was found to be physiologically fully as active as the natural fraction. Harington and Barger[89] suggested that thyroxine is probably synthesized *in vivo* by the iodination of tyrosine followed by the oxidative coupling of two molecules of diiodotyrosine and the elimination of one side chain. Three organic iodine containing compounds are present in the thyroid gland: diiodotyrosine, thyroxine and thyroglobulin. In addition the non iodine containing amino acid tyrosine is present. This compound is the basic amino acid from which the hormone is formed and is present in the thyroid in roughly inverse proportion to the concentration of diiodotyrosine and thyroxine.[90] Inorganic iodine acts on the tyrosine to form diiodotyrosine. Two molecules of diiodotyrosine are then coupled with the loss of one side chain to form a molecule of thyroxine. Finally, thyroxine and diiodotyrosine are then linked through an amino acid to form thyroglobulin.[91] Thyroglobulin is a large molecule with a molecular weight of approximately

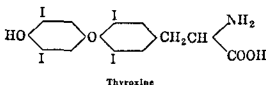
700 000 [92] About one third of the iodine in thyroglobulin is combined as thyroxine and the remainder as diiodotyrosine The presence of iodine is an exceedingly important factor in determining the thyroxine like activity of the molecule *Thyronine* is thyroxine from which the 4 iodine atoms have been removed and replaced by hydrogen With the total removal of the iodine the thyroidal activity of the compound is completely lost *Diiodothyronine* which is thyronine minus two iodine atoms, is approximately one fortieth as active as thyroxine [93]



Thyronine



Diiodotyrosine



Thyroxine

With the awareness of the role that iodine plays in rendering these compounds active attempts were made to form thyroxine like substances by the simple iodination of nondescript proteins Ludwig and von Mutzenbecher[94] finally succeeded in isolating crystalline thyroxine from iodinated proteins This observation was promptly confirmed by Harington and Pitt Rivers [95] Somewhat earlier Salter and Lerman[96] had produced proteins which were capable of correcting human myxedema by the simple treatment of albumin with iodine *in vitro*

It promptly became evident that protein was essential for the synthesis of thyroxine both *in vivo* and *in vitro* The type of protein is apparently a matter of indifference provided one of its amino acid constituents is tyrosine which in the presence of elemental iodine will form thyroxine Various protein hydrolysates have been successfully used in the synthetic production of thyroxine Casein which is perhaps the most satisfactory contains 5 65 per cent of tyrosine If all the tyrosine were iodinated and subsequently converted to thyroxine the calculated yield of the latter would be about 10 6 per cent Actually iodinated casein containing 3 per cent of thyroxine like substance can be regularly prepared but the yield beyond this point has not as yet been increased [97]

Thyroxine when administered intravenously exercises a prolonged effect but surprisingly enough the hormone itself is rapidly withdrawn from the blood stream Gaebler and Strohmaier[98] injected 10 mgm of thyroxine

intravenously into dogs and found that three minutes after the injection iodine titration showed that only half of the injected dose was still present in the blood stream and within twenty four hours over 90 per cent had disappeared *from the blood*. *Leblond*[99] *found that with the injection* of minute physiologic amounts of radioactive thyroxine into the rat only about 2 per cent of the injected material remained *after two hours*. This disappearance of thyroxine from the circulation apparently does not affect its activity since it is not destroyed but rather withdrawn under the influence of other organs. According to Leblond[99] the injected radioactive thyroxine in the rat is distributed mostly in the liver, small bowel, muscle, skin and large bowel contents. This author could not confirm previous impressions of the specific fixation of thyroxine in the hypophysis or in any of the other endocrine glands. Only minute amounts of the injected radioactive thyroxine enters the thyroid gland.

Albert and Keating[100] administered radioactive dl-thyroxine both by *mouth and by the intravenous route to two patients with myxedema*. Although the oral administration of thyroxine is said to be ineffective their patient responded well and the metabolic behavior of the radioactive thyroxine thus administered was indistinguishable from that given intravenously. Their conclusions are as follows: On entry into the circulation thyroxine is *confined at first to the plasma from which it is transferred* to the tissues of the body including especially such organs as the liver and becomes equilibrated with the thyroid hormone already present in tissue. In the tissues thyroid hormone is catabolized mainly to iodide and to a minor extent is split apparently at its ether linkage. The iodide liberated becomes equilibrated with serum iodide and is present as only a small percentage of the total serum iodine partly because it is disposed of *rapidly and partly because its volume of distribution is comparatively* large. The liberated iodide present in blood is eliminated mainly in the urine. Thyroid hormone is not *accumulated by the thyroid* and reutilized. Iodide liberated in the catabolism of thyroid hormone is reaccumulated and reutilized in a normal person. Approximately 20 per cent of the liberated iodide would be accumulated by the normal thyroid. The bulk of thyroid hormone is therefore deiodinated and excreted in the urine as iodide. A small almost negligible amount of thyroid hormone appears to be excreted unchanged and another small portion as a split product similar in behavior to diiodotyrosine. Perhaps as much as a third or more of the thyroid hormone is excreted in the feces in protein bound form.

As mentioned previously, injected thyroxine exercises a prolonged effect which becomes evident in the human within twenty four to forty-eight hours, reaches a peak in seven to ten days and then subsides slowly. The effect of a single dose may persist for from three to ten weeks.[101] The administration of one mgm. of thyroxine intravenously will increase the *basal metabolic rate of a normal adult* by 2.8 per cent. Larger doses will increase the metabolism proportionately.[3]

The Physiologic Effects of the Thyroid Hormone.—Our knowledge concerning the physiologic action of the thyroid hormone has developed essentially as a result of studies in (1) experimental and clinical myxedema, (2) clinical hyperthyroidism and (3) experimental and clinical use of thy-

roxine and thyroid extract As a result of such studies it has become evident that the thyroid hormone (1) exercises an effect on the rate of oxidation of all cells its so-called calorigenic effect, (2) influences growth and maturation (3) influences salt and water metabolism, (4) affects carbohydrate, protein and lipoid metabolism, (5) influences the function of the neuromuscular system, and through these various functions it (6) influences the circulatory dynamics Finally the thyroid hormone exercises a definite effect on (7) the tegument and (8) the other endocrine glands

Following the experimental ablation of the thyroid gland, there occurs a decrease in the basal oxygen consumption that is the rate of cellular oxidation is reduced This is a fundamental phenomenon which occurs in both animals and man This reduction in oxygen consumption is associated with a decrease in nitrogen excretion in part due to a decrease in the catabolism of food The latter is evidenced by the facts that the specific dynamic action following the ingestion of protein is reduced and that tissue slices from a thyroidectomized animal consume less oxygen than normal [8] The antithesis of this is equally true The parenteral injection of thyroxine causes a significant increase in the oxygen consumption of excised rat liver kidney and striated muscle [102, 103] These observations were confirmed by McEachern in experimentally induced hyperthyroidism [104]

The Effect of the Thyroid on Electrolyte Metabolism —Following total thyroidectomy in the experimental animal and myxedema in man there is a retention of salt and water and an increased deposition of a collagenous material probably mucoprotein in character and probably derived from ground substance The fluid and electrolytes thus retained are mostly extracellular in location and interestingly enough are associated with a considerable reduction in plasma volume and an increased concentration of serum and spinal fluid proteins [105, 106] Following the administration of thyroid hormone to the thyroidectomized animal and the patient with myxedema there occurs a pronounced salt and water diuresis with an increase in the plasma volume These effects are much less evident in the intact animal and normal individual The administration of the thyroid hormone also results in an increase in the urinary excretion of nitrogen Since this increase in the urinary nitrogen is accompanied according to Albright [107] by proportionate amounts of phosphorus and potassium it is probable that the increased nitrogen excretion is mainly due to break down of cells The studies of Byrom[108] would suggest that in myxedema the fluid loss following the administration of thyroid hormone is probably extracellular in origin since it is accompanied by proportionate amounts of the extracellular base sodium In normal individuals there is an increase in the urinary excretion of potassium following the injection of thyroxine Since potassium is the predominant intracellular base whatever diuresis is thus induced probably in part represents loss of intracellular fluid However the role of the mucoproteins as a possible source for both the fluid and nitrogen loss in the myxedematous state following the injection of thyroxine has by no means been adequately studied

In experimental and clinical hypothyroidism there is a decrease in the urinary and fecal excretion of *calcium* and *phosphorus* with an increase in the skeletal retention of these ions. Following the administration of the thyroid hormone and in patients with spontaneous hyperthyroidism there is an increase in the excretion of calcium and phosphorus, although in neither instance is there any change in the serum concentration of these ions.[109] Low and his coworkers[110] have shown that the alterations in calcium and phosphorus metabolism are independent of the phosphatase activity in the bones. Our group[111, 112] has demonstrated an increase in the percentage of bound *magnesium* in the serum of patients with thyrotoxicosis, while in myxedema almost all of the serum magnesium exists in an ionized state. *In neither condition is there any change in the total serum magnesium.* These observations were subsequently confirmed by Levietis and Dine.[113]

The Effect of the Thyroid Gland on Carbohydrate Metabolism.—The role of the thyroid in carbohydrate metabolism is not entirely clear. Patients with hyperthyroidism will often manifest mild hyperglycemia and occasionally glycosuria. The glucose tolerance curve is generally normal, however, except for a prompt high rise after the oral administration of glucose. In experimental and clinical hyperthyroidism alimentary glycosuria is not uncommon. Studies of the respiratory exchange following the administration of glucose, however, indicate that patients with hyperthyroidism are capable of oxidizing sugar as rapidly as normals do.[114, 115, 116] In part, then, the postabsorptive hyperglycemia is probably the result of the accelerated absorption of sugars from the intestinal tract.[117] Coggeshall and Greene[118] have shown that thyroid feeding will cause a depletion of liver glycogen in both the starved and carbohydrate fed experimental animal. They further demonstrated that the administration of glucose failed to replenish the stores of hepatic glycogen in the starved thyroid treated animals. Althausen[117] suggested that the increased peripheral oxidation of sugar leads to the depletion of the glycogen stores in the liver.

The Effect of the Thyroid Gland on Lipoid Metabolism.—In general the serum cholesterol tends to be elevated in hypothyroidism and decreased in hyperthyroidism.[119, 120] In the latter state particularly, however, the level of the serum cholesterol is of relatively little diagnostic import, since the values encountered are so frequently within the normal range. In hypothyroidism the serum cholesterol is usually elevated, especially when the serum precipitable iodine is below 4 gamma per cent.[121] However, the frequency with which normal serum values are encountered in frank hypothyroidism precludes this determination from being of diagnostic value except in a confirmatory manner. Several auxiliary factors besides the degree of functional activity of the thyroid are involved in the regulation of cholesterol metabolism. One of the important extrathyroidal factors is malnutrition. Although thyroidectomy in the experimental animal is regularly followed by hypercholesterolemia, this may be prevented by dietary restriction.[122, 123]

The free cholesterol total cholesterol ratio remains constant at 0.24 to 0.36 in patients with disorders of thyroid function except when complicated by hepatic disease or diabetes mellitus.[121] The neutral fat level of the serum is unaffected by thyroid disease. This fraction may also be ele-

vated when other pathologic states such as diabetes mellitus, renal disease and hepatic impairment complicate the underlying thyroid dysfunction. The ratio of cholesterol to phospholipid phosphorus is similarly unaffected by thyroid disease according to Peters and Man.[14] When the serum cholesterol is within the normal range the ratio remains unaltered in patients with hypothyroidism, euthyroidism, or hyperthyroidism. When the serum cholesterol level is reduced, the ratio falls. This is similar to the findings in malnutrition from any cause. When the serum cholesterol concentration is elevated, the ratio increases.[14] In general then the phospholipid phosphorus rises and falls with the serum cholesterol. The ratio between the two is altered somewhat with the absolute level of the serum cholesterol, but is independent of the underlying disease.

The Effect of the Thyroid Gland on the Circulation.—In hyperthyroidism there is a rapid pulse, a rapid circulation time, and frequently irregularity of cardiac rhythm. In hypothyroidism, on the other hand, the pulse and circulation time are both slowed. There is a good deal of experimental data to explain these and other phenomena encountered in clinical disorders of the thyroid.

The increased metabolism attendant on overdosage with thyroid or in clinical hyperthyroidism calls forth an increase in cardiac output accompanied by a tachycardia, increased stroke volume and vasodilatation. However, the effect of thyroid administration consists of more than its secondary effect on the circulation resulting from the increase in total body metabolism. The thyroid hormone exerts a direct effect on the heart.[1, 131] The glycogen content of the heart muscle may be markedly depleted in experimental hyperthyroidism.[132, 133] The tachycardia induced by thyroxine administration is greater than that induced by an amount of dinitrophenol with comparable effects on the increase in oxygen consumption. The excised heart of an animal poisoned with thyroxine will beat as much as 50 per cent more rapidly than the normal heart.[18] The excised heart *per se* is not affected by the addition of thyroxine to the perfusate, but thereafter this preparation exhibits an increased response to epinephrine. This effect is equally manifested by the thyrotoxic heart *in situ*.[19] Apparently the administration of thyroid hormone blocks the action of the vagus on the heart and increases the effects of epinephrine.[130] The evidence would seem to indicate that the thyroid alters the responses of the sympathetic nervous system. As a result of thyroid administration the effects of epinephrine are enhanced, and following thyroidectomy the response to epinephrine is markedly diminished.[16] At the higher metabolic level which follows the administration of thyroid hormone, the efficiency of the circulation is impaired. With the increase in metabolic rate there is a shift in the oxygen dissociation curve facilitating delivery of oxygen to the tissues.[17] However, the arteriovenous oxygen difference is decreased.[134]

The Effect of the Thyroid Gland on the Neuromuscular System.—In clinical hyperthyroidism there is emotional instability, hyperactivity, muscle tremor, nervousness and irritability. Quite the opposite is noted in hypothyroidism where psychomotor retardation and mental obtundation are the rule. Comparable effects may be induced in the experimental animal by thyroid administration or by thyroidectomy. Further evidences

of nervous system alterations are the manifestations of autonomic imbalance observed in thyrotoxicosis: intestinal hyperperistalsis, sweating, and vasomotor instability. Alterations in muscular function are represented by the severe myasthenia and creatinuria that may occur in clinical hyperthyroidism. The brain tissue participates in hyperthyroidism. Acceleration of cortical alpha rhythms are noted in this disorder, where as retardation is observed in myxedema.[135] In hyperthyroidism the rate of oxidation of brain tissue is greater than in normals and the addition of various substrates such as glucose, fructose, and lactate is attended by a much more marked increase in respiration than occurs in the normal.[136]

The Interrelationship of Thyroid Function and Vitamin Metabolism.— Thyrotoxicosis increases the minimal vitamin requirements of the patient and experimental animal and consequently latent or obvious clinical vitamin deficiencies may ensue. However, in addition to the general or nonspecific effects of vitamin deficiency on bodily metabolism, there may be noted specific effects of inadequate or excessive intake of the vitamins on the thyroid gland. This subject was quite completely reviewed by Drill[137] but since his review some additional observations have been reported.

Vitamin A deficiency will result in thyroid hypertrophy in the female rat but will produce atrophy in the male rat.[139] However, in such a deficient state, although the uptake of radioactive iodine is unaltered, the formation of thyroxine is decreased in spite of any increase in thyroid weight that might ensue.[144] In excessive doses, vitamin A will result in depletion of the colloid content of the gland.[140] It will delay the metamorphosis of tadpoles.[141] It will prevent a number of the toxic effects of thyroid administration such as weight loss, the enhanced toxicity of acetonitrile, and the depletion of muscle and liver glycogen. In addition it will reduce the creatinuria of thyroid intoxicated animals. It is said to reduce the thyrotropic potency of the pituitary and to inhibit the action of thyrotropin. Clinically and experimentally, vitamin A has been reported to reduce the increased oxygen consumption noted in the patient with hyperthyroidism[138] and the thyroid intoxicated experimental animal. As a possible explanation for these effects of the vitamin it has been suggested that it competes with the thyroid hormone for iodine and thereby is produced an iodinated vitamin without the metabolic effects of thyroid hormone but which can depress thyrotropin formation.[14] Another explanation suggested by Sadhu is that hypervitaminosis A depresses the hepatic inactivation of thyroxine.[146, 147, 148] The blood protein bound iodine may be thus increased but the secretion of thyrotropin is inhibited with a resultant decrease in thyroid size and a decrease in the protein bound iodine in the gland. In the thyroidectomized animal the burden of evidence would indicate a decreased ability to convert carotene to vitamin A.[144, 145, 150, 151] As a result of this the symptoms of carotenemia and vitamin A deficiency may ensue.

Although in clinical and experimental hyperthyroidism the requirements for the B complex fractions, especially thiamin, are markedly increased, there appears to be no specific thyroidal effect of this vitamin group. In hyperthyroidism weight loss, hepatic damage, and loss of liver glycogen

are noted If adequate doses of B complex, as in yeast or liver,[1,3] are administered these effects may be prevented or minimized The prevention of weight loss is in part due to the increased caloric intake attendant on the stimulation of appetite by these vitamin fractions Recent studies have revealed that the greater beneficial effects of liver and yeast[152,153] as compared to diets containing the purified fractions of the B complex might be due to B_{12} which was not supplied in the latter synthetic diets [154] If thiamin deficiency is produced the tachycardia of hyperthyroidism decreases In hyperthyroidism, the tissues are depleted of the components of the B fraction at least of thiamin and riboflavin, and the excretion of these fractions is increased

There is an increased requirement also for ascorbic acid in hyperthyroidism Although vitamin C has been reported to reduce the basal metabolic rate in experimental hyperthyroidism its specific effects on thyroid function are still controversial Recent evidence[149] would tend to deny any such effects The administration of ascorbic acid will however, reduce the creatinuria encountered in the animal with experimental hyperthyroidism, but has no effect on the depletion of liver glycogen Scurvy especially in the chronic state results in hyperplasia and hemorrhagic infiltration of the thyroid gland in the guinea pig

Avitaminosis D is without specific effect on the thyroid gland Excessive dosage of this vitamin however may increase the basal metabolic rate Although in the experimental animal with hyperthyroidism, vitamin D administration will decrease the negative calcium balance by diminishing the fecal loss no such effect has yet been observed in Graves disease

The Interrelationship Between the Thyroid and the Other Endocrine Glands —Effect on the Hypophysis —Thyroidectomy results in the production of signet ring cells in the adenohypophysis [158] These cells are characterized by multiple small vacuoles occurring in the basophils In addition in the rat the eosinophils tend to decrease in number The administration of thyroid hormone readily reverses these cellular changes The changes encountered after thyroidectomy are noted also following the experimental induction of hypothyroidism with goitrogenic diets such as those containing the thioureas [157,159,160]

Contrariwise the administration of thyroid hormone to the intact animal results in atrophy of the pituitary[155] and a loss of thyrotropic content [156]

The Interrelationship Between the Thyroid and Adrenal —The administration of epinephrine may induce hyperplastic changes in the thyroid [161] The physiologic effect of epinephrine on the thyroid gland is most easily studied in the adrenalectomized animal where following the administration of adrenalin the uptake of I_{131} is increased [162] In the intact rat however epinephrine results in a decreased uptake In the patient with pheochromocytoma the basal metabolic rate is often elevated and the thyroid gland is moderately hyperplastic

Hyperfunction of the adrenal cortex may result in decrease in thyroid function presumably due to a decrease in the secretion of thyrotropin Evidence for this includes the diminution of uptake of I_{131} by the thyroid following epinephrine administration to the intact rat and the decrease in I_{131} collection following cortisone administration to the epinephrine

treated adrenalectomized rat Further the basal metabolic rate of patients with Cushing s syndrome is often reduced

Bomskov and Schneider[164] claimed that the thyroid of adrenalectomized animals dying shortly after operation showed evidences of hyperthyroidism and the thyroids of surviving animals underwent atrophy Following adrenalectomy there is an increased heat production which is prevented by prior thyroidectomy [165] In addition adrenal injury results in a rapid loss of thyroidal iodine In the patient with Addison s disease there frequently is atrophy of the thyroid and a decrease in basal metabolism The adrenalectomized animal is extremely sensitive to thyroid administration [166]

The administration of thyroid hormone by mouth or parenterally will result in adrenal cortical hypertrophy [167] due to hypertrophy and hyperplasia of the cortical cells in all three layers However if thyroid is fed to a pregnant animal the adrenals of the fetus are decreased in size [48] Thyroxine reduces the ascorbic acid content of the cortex[169] and depletes the cortex of its steroids [170] Similarly in short term experiments the cholesterol content is depleted but after a long period of treatment the subsequent adrenal hypertrophy results in an increase of the total cholesterol content of the gland [172] Thyroxine increases the compensatory adrenal hypertrophy following unilateral adrenalectomy [171] but not in the hypophysectomized rat [172] Thyroid development in the embryo is retarded by adrenal cortical implantation [174]

In the patient with hyperthyroidism however narrowing and degeneration of the adrenal cortex is noted frequently [175]

Thyroidectomy in the rat is followed by reduction in the size of the adrenal [176, 177, 184] In the pregnant guinea pig however thyroidectomy induces enlargement of the fetal adrenals [168] Following thyroidectomy degeneration of the cortical cells ensues [178] and the lipid and ketosteroid content are decreased especially in the fasciculata [170] Similar findings are noted after treatment with thiouracil [170, 179, 184] The retardation of tooth eruption and opening of the eyelids in baby rats following thiouracil administration can be prevented with desoxycorticosterone but this compound has no effect on the stunting of body growth resulting from the former drug [180] Compound E cannot exert its full effect on protein metabolism in the absence of thyroxine [181] Recent evidence indicates that hypothyroid rats are unable to respond adequately to stress [182, 184, 185] Whether this is due to failure to elaborate ACTH or failure of the adrenal cortex to respond to ACTH [183] or the failure of the end organs to respond to corticosteroids in the presence of a hypothyroid state is as yet unanswered

In both hyperthyroidism and hypothyroidism the urinary excretion of the neutral 17 ketosteroids is reduced In hypothyroidism the 11-oxygenated steroids are also reduced

The Interrelationship Between the Thyroid and Gonads —Circumstantial clinical evidence would lead one to suspect an interrelationship between the gonads and the thyroid but experimental proof is rather meager Hyperthyroidism is not uncommonly precipitated at the menopause and colloid goiter not infrequently develops during puberty These effects of course may be hypophyseal in origin rather than related to altered gonadal function For many years gynecologists have employed thyroid

extract for a wide variety of gynecologic disorders, with little rationale. Recently, however, it has been demonstrated that spontaneous abortion may be correlated with low levels of the serum precipitable iodine in the mother.[186]

Castration or cryptorchidism in the rat may be associated with a decrease in the size of the thyroid.[187] In the castrate the pituitary becomes enlarged but in the cryptorchid the pituitary size is the same as in the normal control. Aron and Benoit[189] however claim castration results in increased thyrotropin secretion and the administration of estrogens may inhibit thyrotropin action.[60] Gonadectomy in the guinea pig is reported[190] to result in thyrotropin secretion and thyroid proliferation. In thyroidectomized ducks and cocks[188] the testes shrink rapidly and spermatozoa formation stops. Similar findings are observed in the rat.[194] Thyroid feeding stimulates the gonads of immature male ducks to activity.[189] Furthermore the pituitary implants from normal illuminated ducks exhibit gonadotropic activity whereas similar implants under identical circumstances from thyroidectomized ducks fail to demonstrate gonadotropic activity in mice. Rats fed thyroid have greater gonadotropic potency in their pituitaries than do thyroidectomized litter mates.[193,195] The administration of thyroid to rats[195] may result in increased size of the testes although the accessory reproductive organs may be diminished in size.

In immature male rats made hypothyroid by thiouracil the response to pituitary gonadotropin is increased and when the immature rat is fed thyroprotein the response is decreased. On the other hand thiouracil reduced the response in the immature mouse but thyroprotein increased the response.[196]

In adult mice the administration of testosterone induces hyperplastic changes and diminution of colloid.[191] Further evidence along this line was adduced by the demonstration that the administration of testosterone increases the number of mitoses in the thyroid epithelium.[197]

In the thyroidectomized monkey amenorrhea ensues. This is corrected by the administration of thyroid.[197] Menorrhagia however may result and this is far more frequent in the hypothyroid than in the euthyroid monkey. An amount of estrogen sufficient to produce bleeding in the intact animal will not result in bleeding in the ovariectomized thyroidectomized animal unless thyroid is also given. In rams the lowering of reproductive activity by high environmental temperatures is reversed by the administration of thyroproteins. The normal reproductive activity is inhibited by thiouracil. The resultant clinical state simulates the effects of high environmental temperature.[198]

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tension[3,4] and tremor due to various causes are some of the clinical states which *may* yield abnormally elevated readings Undue effort before the test and an inadequate postprandial period anxiety and various subjective factors may influence the basal metabolic rate

In reviewing the available data in the literature of reports comprising approximately 2000 patients with proven thyrotoxicosis the basal metabolic rate was less than +20 per cent in 11 per cent[5,6,7] This of course included data from several clinics and hence by no means constitutes an adequately controlled study Actually the results varied from 2 per cent in 600 patients[6] where the basal metabolic rate was less than +20 per cent to 22 per cent of 171 patients with similar results[7] The largest series of this group was reported by Means[5] who found that of 1 164 cases of thyrotoxicosis 12 per cent of the females and 8 per cent of the males had basal metabolic rates of less than +20 per cent In our own experience at the Mount Sinai Hospital of 500 patients with proven thyrotoxicosis the basal metabolic rate was less than +20 per cent in slightly less than 5 per cent There are fairly large individual groups of hyperthyroidism reported with normal or even low basal metabolic rates Davison[8] described 60 cases of thyrotoxicosis with readings between −37 and +12 per cent and Hendrick[9] reported 47 patients with rates which varied between −26 and +13 per cent

The reasons for the normal results obtained in patients with proven hyperthyroidism are for the greater part obscure One of the factors is the level of the basal metabolic rate of the patient before the onset of thyrotoxicosis An individual whose basal metabolic rate prior to the onset of the disease was −15 per cent or less may with the development of a relatively mild degree of thyrotoxicosis show an increase only slightly beyond the accepted normal range but which still constitutes a considerable increase *for this particular patient* The severity of the disease bears only a rough relationship to the basal metabolic rate By far and large however patients with less severe manifestations and those with pronounced exophthalmos associated with otherwise minor constitutional symptoms will show lesser degrees of elevation of the BMR The role of the widespread dietary use of iodized salt in these discrepant findings may be significant In any event regardless of the cause it is pertinent to bear in mind that approximately 5 to 10 per cent of patients with thyrotoxicosis will show readings relatively within the normal range

The results of the basal metabolic rate are much more consistent in myxedema Although there are other causes for a reduction in the BMR it is unusual not to find a marked lowering in patients who present the classical manifestations of the disease Of 25 patients reported by Skanse[7] only one had a normal basal metabolic rate Means[5] emphasizes that the failure to find a metabolic level as low as −35 per cent in the presence of a clear-cut picture of myxedema is very unusual Generally most patients with this illness will have metabolic readings which fall into the range of −25 to −45 per cent

The significance of modest reduction in the basal metabolic rate is more obscure There are so many factors physiologic and otherwise which may produce a decrease in the basal metabolic rate which in some instances

Chapter 23

THE VALUE OF LABORATORY AIDS IN THE DIAGNOSIS OF THYROID DISEASE

THE BASAL METABOLIC RATE, SERUM CHOLESTEROL, SERUM PROTEIN BOUND IODINE (*SERUM PRECIPITABLE IODINE*), *THE THYROID UPTAKE OF RADIOACTIVE* IODINE, THE URINARY EXCRETION OF RADIOACTIVE IODINE, PROFILE STUDIES AND RADIOAUTOGRAPHY FOLLOWING THE ADMINISTRATION OF RADIOACTIVE IODINE, SPONTANEOUS CREATINURIA AND THE CREATINE TOLERANCE TEST, MAGNESIUM PARTITION STUDIES, CIRCULATION TIME, THE THERAPEUTIC RESPONSE TO IODINE

The recognition of thyroid disease is primarily the function of the clinician and not of the laboratory technician. No single test or battery of tests can completely replace clinical judgment either in the recognition of the existence of thyroid dysfunction or in the progress of such disease. None of the tests available today can unequivocally determine the presence or absence of thyroid disease, but rather they serve to supplement the clinical impression and in doubtful instances to lend weight in the proper diagnostic direction.

The following are the tests available for the determination of the status of thyroid function:

1. The basal metabolic rate
2. The serum cholesterol
3. The protein bound iodine in the serum
4. The thyroid uptake of radioactive iodine
5. The urinary excretion of radioactive iodine
6. Magnesium partition studies
7. The creatine tolerance test
8. The therapeutic response to iodine

The Basal Metabolic Rate.—If we accept −10 to +15 per cent as the normal range for the basal metabolic rate, we find that the BMR is elevated in most patients with hyperthyroidism and reduced in most instances of hypothyroidism and myxedema. However, normal basal metabolic rates are found in patients with clinically frank hyperthyroidism and even more frequently in instances in which the Graves' disease is masked or borderline. Similarly, moderately elevated basal metabolic rates may be encountered in illnesses and clinical states unrelated to thyroid disease. Finally, technical errors which incidentally are a hazard inherent in all laboratory procedures may distort the results. Fever, dyspnea due to pulmonary or cardiac disease, severe anemia, leukemia, polycythemia, Hodgkin's disease, lymphosarcoma, coarctation of the aorta,[1] aortic stenosis,[2] essential hyper

an increased amount of circulating thyroid hormone and hence indicated increased thyroid activity, while values of less than 3.0 μ per cent occurred in hypothyroidism and myxedema. In normal adults this organic iodine fraction tends to remain relatively constant, although a slight increase does occur during pregnancy.[3]

In the determination and interpretation of the serum protein bound iodine there are several possible sources of error which may yield misleading results. 1. The technic itself is difficult in the sense that it requires meticulous technical care and a laboratory free from iodine vapor or fumes. 2. The administration of thyroid extract or thyroxine will cause an increase in the serum concentration of the protein bound iodine fraction which may erroneously be interpreted as evidence of thyrotoxicosis. 3. The use of organic iodine dyes for roentgenologic visualization will cause a marked increase in the protein bound fraction in the serum. Following intravenous pyelography, the elevation in the organic iodine fraction in the serum will subside after several days. Cholecystographic visualization, on the other hand, will result in an increase in the serum organic iodine fraction that may last for weeks or even many months. It is important in instances in which the serum protein bound iodine fraction is elevated and inconsistent with the clinical picture to question carefully as to the previous administration of dyes for purposes of *x* ray visualization. 4. Finally, the administration of inorganic iodine or the thiourea compounds to patients with thyrotoxicosis will sometimes, although not always, cause a decrease in the protein bound iodine.[4, 7]

The results obtained with the use of the serum protein bound iodine as an index of thyroid activity have been very satisfactory. In an analysis of 543 cases of thyrotoxicosis gathered from the literature, cases in which the serum precipitable iodine was determined, the values were above 8.0 micrograms per cent in 94 per cent.[7, 4–8] These values, of course, represent over-all results obtained from more than one laboratory utilizing varying technics. It is astonishing, however, how reasonably similar to one another the results from the various groups have been. In general, the serum levels of the protein bound iodine have been more uniformly elevated in patients with frank thyrotoxicosis than in those instances in which the clinical picture was less well defined but in which the existence of hyperthyroidism was definitely established by the subsequent course of events. This phenomenon is true of all tests of thyroid function, and indeed of all tests. The clinically borderline cases are most likely to yield equivocal results.

Where there has been an opportunity to compare the results obtained with the serum protein bound iodine and the basal metabolic rate, it was found that the former yielded a considerably greater percentage of correct results consistent with the clinical impression. Of 415 cases of hyperthyroidism where comparable studies were conducted, the values of the serum precipitable iodine were consistent with the diagnosis in 92 per cent, while this was true of the basal metabolic rate in 84 per cent.[7, 5, 6, 7, 8]

The results obtained in myxedema are perhaps even superior to those seen in thyrotoxicosis. In 98 per cent of the patients with myxedema the serum protein bound iodine was less than 3.0 micrograms per cent.[7, 2, 5]

may be considerable that the diagnosis of hypothyroidism on this basis alone in the absence of suggestive clinical signs and symptoms is not justified

Serum Cholesterol —It has been demonstrated experimentally in both animals and man that total thyroidectomy is followed by the development of hypercholesterolemia [10–13] In hyperthyroidism on the other hand there is a tendency for the serum cholesterol to be reduced [14 15] These reports in general refer only to trends, but as a matter of actual experience in individual cases of hyperthyroidism and to a much lesser extent in hypothyroidism, the determination of the serum cholesterol concentration is of relatively little value Skanse[7] in a series of 122 patients with thyrotoxicosis reported that in 109 patients the serum cholesterol level fell within the normal range Similar findings were reported by Peters and Man [13] and by Foldes and Murphy [16] The results are somewhat more diagnostic in hypothyroidism but still leave a good deal to be desired Of 26 patients with frank myxedema reported by Skanse [7] 19 showed a considerable elevation in the serum cholesterol concentration but 7 fell well within the normal range

Our own experience has been similarly unrewarding With a normal range for total serum cholesterol which varies from 150 to 240 mgm per cent most of our patients with thyrotoxicosis fell well within this range level Perhaps the major value of the serum cholesterol determination is its possible use as a guide in therapy Hurxthal[17 18] has emphasized the fact that the serum cholesterol level rises during the successful treatment for hyperthyroidism and falls following the therapeutic response in myxedema

The Protein bound Iodine of the Serum —The protein bound iodine concentration of the serum or plasma is a very sensitive index of thyroid function and reflects the level of the circulating thyroid hormone The concentration of the total blood iodine on the other hand is much less satisfactory as a test of thyroid activity since there is such considerable overlapping between the pathologic and the ostensibly normal thyroid states Perkins and Lahey [19] determined the total whole blood iodine values in 1 078 consecutive patients with hyperthyroidism and in 745 patients with no evidence of thyrotoxicosis The overlap between the two groups was considerable Several years later Curtis and Fertman[20] found that in 45 per cent of 142 thyrotoxic patients the whole blood iodine value fell within the normal range This has become the general experience and for the greater part most laboratories and clinics now utilize the protein bound iodine (serum precipitable iodine) rather than whole blood iodine as a test of thyroid activity It is a matter of indifference as to whether serum or plasma is used for the determination of the protein bound fraction [1]

The normal values for the protein bound iodine of the serum or plasma vary from 3 to 8 micrograms (gamma) per cent Riggs [2] in 400 consecutive analyses considered 3 5 to 7 0 micrograms (μ) per cent as the normal range Values between 3 0 and 3 5 and 7 0 and 7 5 this investigator considered to be borderline Winkler [1] in a study of 235 normal individuals considered the normal range to vary between 3 0 and 8 0 micrograms (μ) per cent Serum values above 8 0 micrograms (μ) per cent were indicative of

holder. An important source of error in the use of this technic is the possible disparity between the size of the gland and the dimensions of the aperture of a given Geiger counter. It is important that the Geiger counter aperture be wide enough to include the entire gland. Since the size of the gland varies very considerably in different patients and its approximate dimensions are not always accurately determinable by palpation, the use of a proper sized counter may be difficult. A suitably large counter with a wide enough aperture to cover almost every type of gland is, however, not satisfactory for localization within or measurement of uptake in part of the gland. On the other hand, a small counter placed directly against the neck is desirable for this purpose but is unsatisfactory for the overall uptake measurement.[20] Uptake is determined by measurement of the gamma rays. The beta rays, which are highly localized, are absorbed within 2 millimeters of tissue and do not pass through the skin. These qualities of the beta rays make them useful for therapeutic purposes but unsatisfactory for measurement of uptake in diagnosis. The gamma rays pass through the skin and are readily detected by the Geiger counter and hence are used for diagnostic purposes, but contribute to a much lesser extent than the beta rays to therapy. The normal value for the uptake of I_{131} by the thyroid, according to Werner and his coworkers,[20] varies from 10 to 35 per cent of the ingested dose measured twenty-four hours after administration.

The major portion of an ingested dose of radioactive iodine is excreted in the urine within forty-eight hours.[21, 22, 23] Actually, most of the excretion occurs within the first twenty-four hours, a much smaller amount during the next twenty-four hours, and only minute amounts thereafter. Thus, in 110 normal men and women varying in age from fifteen to seventy-four years, Skanse[7] found that the urinary excretion of I_{131} during the first twenty-four hours varied from 39.9 to 81.3 per cent with an average of 60.6 per cent. During the next twenty-four hours, the urinary excretion of the radioactive iodine varied from 0 per cent to 11.6 per cent, with an average of 5.3 per cent. The total forty-eight hour urinary excretion varied from 44.0 to 87.8 per cent, with an average of 65.9 per cent. These values agree well with those suggested by Kelsey, Haines and Keating,[24] who found that in normal persons the kidneys excrete about 60 to 70 per cent of the administered dose within forty-eight hours, at a rate of about 5 to 9 per cent of the circulating radioactive isotope per hour. For clinical purposes, measurement of the urinary excretion of I_{131} may be made either twenty-four hours or forty-eight hours after administration. Both are equally satisfactory. In hyperthyroidism, more radioactive iodine is taken up by the thyroid and less is therefore excreted in the urine. In clinically well-defined hyperthyroidism, Skanse[7] found that the average forty-eight hour urinary excretion of I_{131} was 17.4 per cent, with a range which varied from 1.9 to 38.6 per cent. During the first twenty-four hours the average was 15.5 per cent. Where the hyperthyroidism was less well defined, the range was considerably wider—from 8.4 to 66.1 per cent after forty-eight hours, with an average of 29 per cent. Kelsey and his coworkers[24] reported that the average forty-eight hour urinary excretion of I_{131} in a group of patients with exophthalmic goiter was 23.4 per cent, while in instances of adeno-

Where the clinical picture is equivocal however and the basal metabolic rate only moderately reduced the serum protein bound iodine may be less helpful

The determination of the organic iodine fraction is particularly helpful in identifying instances of hypermetabolism without hyperthyroidism Thus in the leukemias chronic infections with fever chronic pulmonary and cardiac disease polycythemia vera Hodgkin s disease *etc* the elevation of the basal metabolic rate may suggest the existence of thyrotoxicosis but the serum protein bound iodine is usually well within the normal range In an analysis of 412 cases of a variety of diseases including hypo- and hyper thyroidism instances of hypermetabolism not associated with thyrotoxicosis and diseases completely unrelated to the thyroid the results of the determination of the organic iodine fraction of the serum was consistent with the clinical impression in 92 per cent of the instances

The Uptake and Urinary Excretion of Radioactive Iodine —The radioactive isotope I_{131} with a half life of 8 days is the isotope most generally used both in the diagnosis and the treatment of thyroid disease For purposes of diagnosis one may measure either the uptake of this isotope by the thyroid or its excretion in the urine It may be administered either with or without a carrier or inert iodine generally sodium iodide The urinary excretion of I_{131} is usually greater where no carrier is employed The reason for the use of the carrier iodine is to avoid oxidation of the radioactive moiety Since the amount of the latter administered for testing purposes is so minute its chemical alteration when administered alone may conceivably yield misleading results Since I_{131} is now available in slightly alkaline solution oxidation of the iodine does not readily occur following its administration and the use of carrier iodine is hence less necessary The disadvantage of the use of stable iodine as carrier is the fact that its repeated administration in the same patient may conceivably induce a therapeutic effect such as occurs with Lugol s solution and render subsequent testing inaccurate This however is dependent in good part on the amount of carrier iodine used It is conceivable too that where the total carrier iodine ingested is large enough it may subsequently interfere with the effect of radioactive iodine administered for therapeutic purposes These considerations however are largely theoretical since the amount of stable iodine used as carrier is usually very small Actually it does not particularly matter whether carrier iodine is employed or not

For purposes of diagnosis the dosage of I_{131} used varies from 40 to 100 microcuries both for measurement of uptake and for urinary excretion Generally the latter amount is employed Where inert iodine is used as carrier 100 micrograms of sodium iodide is administered with the I_{131} Both the tracer dose and the inert iodine are given orally either before breakfast or in a non fasting state When uptake is being measured such measurements are made twenty four hour after administration of the I_{131} [20] When urinary excretion is being studied determinations may be made either twenty four or forty-eight hours after ingestion of the radio active iodine [7] The uptake of the radioactive isotope is determined by placing the Geiger counter at a standard distance of 15 centimeters from the neck with the thyroid isthmus as a center and the head and neck in a special

results As with the other tests of thyroid function the results are better where the clinical picture of thyrotoxicosis is unequivocal There is a progressive increase in the percentage of false and equivocal results as the clinical manifestations become less well defined although the subsequent course of events may establish the diagnosis of hyperthyroidism In well defined cases of thyrotoxicosis including both toxic diffuse and toxic nodular goiter Werner and his coworkers[19] report that 94 per cent of the group had uptakes of I131 in excess of the normal range of 35 per cent The results reported by Skanse[7] who measured the urinary excretion are even better in that 95 per cent of his patients with hyperthyroidism excreted less than the normal amount

There is no hard and fast specific value however either of uptake or excretion beyond which the results must be considered to be abnormal There is a considerable area of overlapping between the normal and the patients with thyroid dysfunction The interpretation of the results falling in this overlapping or borderline area is dependent then on the clinical picture and the interpretation of the other tests of thyroid function If the patient has definite clinical evidence of thyrotoxicosis a borderline result is considered to be consistent with the clinical impression In the absence of any manifestations of thyrotoxicosis a similar value is interpreted as being within the normal range Unfortunately a fair percentage of patients suspected of suffering from thyrotoxicosis but with an equivocal clinical picture will yield similarly equivocal results with radioactive iodine studies and indeed with the other tests of thyroid function This observation does not detract from the value of the use of radioactive iodine but simply emphasizes the fact that this procedure like other technical procedures has certain limitations which must be borne in mind Of 112 normal individuals and 82 patients with clinically obvious thyrotoxicosis studied at our hospital Feitelberg Silver Wasserman and Yohalem[26] found that 20 per cent of the normal individuals excreted less than 30 per cent of the ingested radioactive iodine within twenty four hours while 5 per cent excreted 20 per cent or less In the patients with hyperthyroidism 15 per cent excreted between 20 and 30 per cent and 2 per cent excreted more than 30 per cent This data would indicate that in 15 to 20 per cent of patients studied there will be an area of overlapping between patients with thyrotoxicosis and any other non thyrotoxic group This is true if we accept a urinary excretion of radioactive iodine of 20 per cent as the dividing line between thyrotoxic and non thyrotoxic cases and is equally true if a urinary excretion of 30 per cent is thus established In the former although only 5 per cent of normal individuals will yield results similar to those observed in hyperthyroidism 15 per cent of patients with thyrotoxicosis will fall within the normal range of excretion If a urinary excretion of 30 per cent is accepted as the dividing point only 2 per cent of patients with thyrotoxicosis will excrete more than this amount but 20 per cent of normal individuals will yield excretion results similar to those obtained in hyperthyroidism

Silver Feitelberg Wasserman and Yohalem[27] further compared the results obtained both with the serum protein bound iodine and the urinary excretion of radioactive iodine in 75 normal individuals and in 75 patients

matous goiter with hyperthyroidism the average was considerably higher 43 6 per cent At our hospital, the urinary excretion of I_{131} is determined at the end of twenty four hours A urinary excretion of 20 per cent or less is considered to be consistent with hyperthyroidism Urinary excretions between 21 and 35 per cent are considered borderline, while values above this level are regarded as falling within the normal range

In hypothyroidism and myxedema, less radioactive iodine is theoretically taken up by the thyroid and more therefore excreted in the urine The average forty-eight hour urinary excretion, according to the report of Skanse [7] is 83 6 per cent which is considerably higher than the normal average When the urinary excretion of the isotope was fractioned this author found that the average twenty four hour excretion was well within the normal range 61 4 per cent but that a considerable increase in excretion occurred during the second twenty four hour period During this latter period the urinary excretion of the I_{131} varied from 15 2 to 34 6 per cent with an average of 22 6 per cent in contrast to 5 3 per cent in normal individuals This curious delay in the urinary excretion of radioactive iodine is, however not specific for myxedema but may also occur in renal and cardiovascular disease In general the results of the urinary excretion of radioactive iodine in myxedema and hypothyroidism are not satisfactory since there is a considerable overlapping with normal values The urinary excretion of I_{131} above 80 per cent after forty-eight hours may be interpreted as consistent with the diagnosis

The urinary excretion of I_{131} may be determined both by beta and by gamma ray counts The report by Freedberg Buka and McManus[35] showed that the results obtained by both counting procedures agreed within 5 per cent The gamma counting method however is by far the simpler one and results are obtained promptly The use of the beta method for urines is cumbersome requiring adjustment of the pH to the alkaline side as well as considerable care to avoid loss from handling the dried samples Finally distortion of results through mass absorption may be an important factor when beta counts are used

There are certain important sources of error in the measurement of the urinary excretion of radioactive iodine If the collection of urine specimens is incomplete the excretion of the isotope will be proportionately reduced The urinary excretion is also influenced to some extent by the presence of renal disease and perhaps congestive failure Hence a low urinary excretion of radioactive iodine is significant provided that the urine collection is complete and that no renal or cardiovascular disease is present which is associated with oliguria Both uptake and urinary excretion are influenced of course by the previous administration of iodine antithyroid drugs thiocyanate and possibly thyroid extract when it is used over a prolonged period of time In all these instances there occurs a decrease in the uptake of radioactive iodine and an increase in its urinary excretion

The results obtained in hypothyroidism and myxedema both by measurement of uptake and urinary excretion of I_{131} are conceded by most investigators to be unsatisfactory and far less dependable than determination of the protein bound iodine of the serum [7,33] The use of radioactive iodine for the diagnosis of hyperthyroidism however yields very rewarding

ments made at ½ inch intervals without changing the level of the tube. Counts per second are plotted against distance from the midline and the resultant graph is referred to as a horizontal profile. Vertical profiles are obtained by moving the tube along the midline or parallel to it and the counts per second are plotted against the distance from the vertex of the skull in inches. In addition to these studies surveys of the chest, back, extremities and pelvis are routinely made for evidences of metastatic uptake. These determinations are not plotted. The curves which are plotted by the profile studies in the neck are helpful in identifying the existence of aberrant thyroid tissue or in identifying hyperfunctioning nodules in one lobe of the thyroid or the other. Thus, with these profile studies the above investigators could determine the existence of aberrant lingual thyroid tissue in one patient, the presence of functioning non-toxic adenoma in one lobe or the other in other patients, and the presence of actively functioning malignant metastatic cervical nodes in still others.

This technic is important in demonstrating the presence or absence of *thyroid tissue and even roughly its relative size and distribution*. However, it cannot be used for the more precise diagnoses of thyroid disease since it is incapable of distinguishing between colloid cysts and metabolically inactive carcinoma and between functioning adenomas and active carcinoma. Finally, it cannot readily distinguish between an inactive tumor surrounded by normal thyroid tissue and an active tumor.[4] Profile studies serve primarily as a preliminary exploratory study and for more definitive information radioautographic studies with biopsy must be resorted to.

The radioautographic technic was originally introduced by Hamilton, Soley and Eichorn.[42] Twenty-four to forty-eight hours before surgical biopsy of the lesion is performed 0.3 to 5.0 millicuries of carrier free I_{131} is given to the patient. Actually radiographic studies may also be done on patients receiving much larger doses for therapy and where operation is subsequently performed usually within two to ten days after the therapeutic administration of the I_{131}.[44] According to Fitzgerald and Foote[44] equally good radioautographic results are obtained when small tracer doses such as 0.3 millicuries are used as when much larger therapeutic amounts are employed. The factor which determines whether a positive or negative radioautograph is obtained is the ability of the tissue in question to concentrate the isotope. Following the removal of the tissue on biopsy approximately forty-eight hours is required for the histologic preparation of the tissue before exposure of the photographic emulsion. According to the technic of Hamilton, Soley and Eichorn[42] a glass slide containing the histologic section of the radioactive tissue is placed against the emulsion surface of a photographic plate or roentgen film. The method of Evans[45] and of Endicott and Yagoda[46] consists of floating paraffin sections of tissue on to the emulsion surface of a photographic plate or *x*-ray film. In this technic the tissue sections remain fixed to the *photographic emulsion during* the process of development and fixation of the film and during the staining of the tissue. The stain employed is a combination of metanil yellow and iron hematoxylin.[44] The duration of exposure is determined by the degree of radioactivity of the tissue section either measured directly or by measure

with subsequently proven hyperthyroidism but in whom at the time of the study the diagnosis was obscure Of the group of patients with hyper thyroidism the protein bound iodine was less than 8 micrograms per cent in only 4 while the urinary excretion of radioactive iodine was more than 20 per cent in 38 patients more than 50 per cent in 17 patients, and more than 35 per cent in 11 members of the group In the normal control series the serum precipitable iodine was above 8 micrograms per cent in 14 individuals and the urinary excretion of I_{131} essentially as described previously It is obvious therefore that both with the serum protein bound iodine and the urinary excretion of radioactive iodine there is a fair degree of overlapping between the normal and thyrotoxic groups The degree of overlapping with both procedures is directly related to the severity and clarity of the clinical picture of thyrotoxicosis Where the diagnosis is clinically obvious both tests will show a high percentage of confirmatory results As the clinical diagnosis becomes more obscure the results of the *tests tend to become less well defined*

In the diagnosis of *factitious hyperthyroidism* that is where the symptoms of hyperthyroidism are induced by exogenous overdosage with thyroid extract or thyroxin the use of the serum precipitable iodine and the urinary excretion or uptake of radioactive iodine is particularly helpful [6, 7] The basal metabolic rate and the serum protein bound iodine are invariably elevated in these instances but the uptake of radioactive iodine is markedly reduced while the urinary excretion of the isotope is considerably increased even above the normal levels The high urinary excretion of radioactive iodine under these circumstances is probably due to the suppression of thyroid function by the administered thyroid extract [38, 39] This disparity between the elevated serum protein bound iodine and the increased urinary excretion or decreased uptake of I_{131} is characteristic of *thyrotoxicosis factitia*

The rate of conversion of I_{131} into serum protein bound radioactive iodine has been used as a test of thyroid function [87, 88, 89] In general the conversion rate is increased in hyperthyroidism and reduced in hypothyroidism According to Sheline and his coworkers[90] this test is of no greater value than the determination of protein bound iodine in the assessment of thyroid function Other investigators however feel that it may offer some advantages over both the usual tracer studies and the orthodox determination of the serum protein bound iodine [91]

Profile and Radioautographic Technics with Radioactive Iodine —The fact that functioning thyroid tissue is capable of concentrating iodine can be used to detect the existence or absence of such tissue anywhere in the body [40, 41] Feitelberg Kaunitz Wasserman and Yohalem[42] described a method for measuring and recording localized collections of administered radioisotopes These authors employed a Sylvania gamma counting Geiger-Muller focus tube enclosed in an open ended lead tube of 1 inch inner diameter made with ½ inch wall thickness Studies were made one to two days after the administration of 0 1 to 0 5 millicuries or more of I_{131} The tube is first placed close to the skin at the level of the thyroid isthmus in the midline and the number of counts per second determined for a one-minute period The tube is then moved laterally to either side and measure

ments made at ½ inch intervals without changing the level of the tube. Counts per second are plotted against distance from the midline and the resultant graph is referred to as a horizontal profile. Vertical profiles are obtained by moving the tube along the midline or parallel to it and the counts per second are plotted against the distance from the vertex of the skull in inches. In addition to these studies, surveys of the chest, back, extremities and pelvis are routinely made for evidences of metastatic uptake. These determinations are not plotted. The curves which are plotted by the profile studies in the neck are helpful in identifying the existence of aberrant thyroid tissue or in identifying hyperfunctioning nodules in one lobe of the thyroid or the other. Thus with these profile studies the above investigators could determine the existence of aberrant lingual thyroid tissue in one patient, the presence of functioning non toxic adenoma in one lobe or the other in other patients, and the presence of actively functioning malignant metastatic cervical nodes in still others.

This technic is important in demonstrating the presence or absence of thyroid tissue and even roughly its relative size and distribution. However it cannot be used for the more precise diagnoses of thyroid disease since it is incapable of distinguishing between colloid cysts and metabolically inactive carcinoma and between functioning adenomas and active carcinoma. Finally it cannot readily distinguish between an inactive tumor surrounded by normal thyroid tissue and an active tumor.[4] Profile *studies serve primarily as a preliminary exploratory study and for more* definitive information radioautographic studies with biopsy must be resorted to.

The radioautographic technic was originally introduced by Hamilton, Soley and Eichorn.[43] *Twenty four to forty-eight hours before* surgical biopsy of the lesion is performed 0.3 to 5.0 millicuries of carrier free I_{131} is given to the patient. Actually radiographic studies may also be done on patients receiving much larger doses for therapy and where operation is subsequently performed usually within two to ten days after the therapeutic administration of the I_{131}.[44] According to Fitzgerald and Foote[44] equally good radioautographic results are obtained when small tracer doses such as 0.3 millicuries are used as when much larger therapeutic amounts are employed. The factor which determines whether a positive or negative radioautograph is obtained is the ability of the tissue in question to concentrate the isotope. Following the removal of the tissue on biopsy approximately forty-eight hours is required for the histologic preparation of the tissue before exposure of the photographic emulsion. According to the technic of Hamilton, Soley and Eichorn[43] a glass slide containing the histologic section of the radioactive tissue is placed against the emulsion surface of a photographic plate or roentgen film. The method of Evans[4] and of Endicott and Yagoda[46] consists of floating paraffin sections of tissue *on to the emulsion surface of a photographic plate or x ray film.* In this technic the tissue sections remain fixed to the photographic emulsion during the process of development and fixation of the film and during the staining of the tissue. The stain employed is a combination of metanil yellow and iron hematoxylin.[44] *The duration of exposure is determined by the degree* of radioactivity of the tissue section either measured directly or by measure-

ment of one cut a few microns away from the one used for exposure[47] Where the tissue section has concentrated a good deal of the radioactive isotope the period of exposure is relatively short In general the less the degree of concentration of I_{131} the longer must the period of exposure be As a rule this period varies from one to three or four weeks and if no radioautograph is obtained at the end of this time it is reasonably good evidence that the tissue being studied is incapable of concentrating the radioactive isotope Exposure is carried out in a light tight box kept at ice box temperature

The use of the radioautograph is important in helping to determine whether nodules in a given thyroid are actively functioning Such activity is manifested by their ability to concentrate radioactive iodine It is significant that some nodules have little or no function, whereas others are capable of concentrating I_{131} avidly Studies with radioautographs have revealed that nodules with excessive function the so-called hyper functioning adenoma' may occur in patients with or without thyrotoxicosis[48, 49] In patients with diffuse toxic goiter, adenomatous nodules present in such a goiter will fail to take up radioactive iodine, while the non adenomatous tissue will show a considerable avidity[44] The antithesis of this is also observed Thus Cope, Rawson and McArthur[50] describe an instance of hyperthyroidism with a single adenoma in which the adenoma took up large amounts of I_{131} while the surrounding non adenomatous tissue was atrophic and collected the radio-active iodine poorly In general then some nodules take up radioactive iodine and others do not When an adenoma manifests a high uptake then as a rule the surrounding non adenomatous tissue is incapable of concentrating radioactive iodine and actually appears atrophic Similarly where the surrounding tissue is functionally active the adenomas will concentrate the isotope poorly[51, 52] Under normal circumstances some balance is apparently automatically established in an effort to secrete only enough thyroid hormone to maintain the euthyroid state

Radioactive iodine is not taken up uniformly either by the normal thyroid or by the thyroid in diffuse toxic goiter[44, 51] There is a considerable variability and patchiness in the amount of radioactive iodine that is concentrated in the colloid of the follicles Adjacent follicles may show extremes in uptake and indeed the smaller follicles may show a heavier concentration of the isotope than do the larger ones Essentially the same situation prevails in instances of multiple adenomatous goiters The adenomas within a single goiter will collect variable amounts of radioactive iodine some more and others less than the surrounding non adenomatous tissue[5]

The use of radioautographs is particularly important in carcinoma of the thyroid since therapy with radioactive iodine is dependent on whether the carcinomatous nodule and its metastases are capable of concentrating the isotope According to Fitzgerald and Foote[44] the concentration of the isotope is related primarily to the presence of colloid The degree with which various carcinomas are capable of concentrating radioactive iodine is paralleled by their colloid content This however is not always true since, as these investigators point out many carcinomatous follicles containing colloid fail to take up I_{131} The uptake of the isotope is as patchy

and variable in the follicles of the carcinoma as it is in the normal or adenomatous gland. The presence of colloid therefore offers no assurance by any means that a particular tumor will be receptive to the radioactive isotope. Fitzgerald and Foote[44] have further described several instances of thyroid carcinoma made up of alveoli containing no colloid which were nevertheless capable of concentrating radioactive iodine. As a general rule, however, those malignant tumors containing colloid are the ones most likely to take up I_{131}. Carcinomatous tissue at best never concentrates more, and usually concentrates less, radioactive iodine than does normal tissue.[44]

One hundred and forty two cases of carcinoma of the thyroid in which radioautographic studies were done were collected from the literature.[44-51] Of these, 63 (44 per cent) collected some radioactive iodine. However, in only about 15 per cent is the concentration of the isotope in the tumor tissue adequate enough to expect some therapeutic effect. This percentage may perhaps be increased by inducing myxedema by various means or by removing normal thyroid tissue which exercises a much more highly selective affinity for the radioactive iodine. Fitzgerald and Foote[44] noted that in 32 cases normal thyroid tissue concentrated the isotope, whereas the malignant tumor in the same radioautographic section failed to take up any radioactive iodine. Rawson and his coworkers[3] found that the concentration of the radioactive iodine in metastatic lesions could be increased by total thyroidectomy. At our hospital, Yohalem, Feitelberg and their coworkers[54] found that of 71 patients with carcinoma of the thyroid, 16 had uptakes of I_{131} either in the primary tumor or in the metastases. In 10 patients who failed to take up any radioactive iodine, myxedema was induced either by surgery or by I_{131}. Of this group, 2 subsequently developed uptake of I_{131} in the metastases where none had been concentrated previously. Uptake of radioactive iodine by thyroid carcinoma and its metastases may perhaps also be increased by inducing hyperplasia of the thyroid carcinoma cells by the administration of antithyroid drugs such as the thiourea compounds, or by the administration of thyrotropic hormone.[55] This method would perhaps be more effective after total thyroidectomy is performed, in order to eliminate competition from normal thyroid tissue.

A hundred cases of thyroid carcinoma were studied with radioautographs by Fitzgerald and Foote.[44] They classified the various types of carcinoma into: 1, the papillary; 2, alveolar and follicular; 3, solid; 4, Hurthle cell; 5, giant and spindle cell; 6, anaplastic; and 7, unclassified groups. The most common type of the series was the papillary carcinoma, and approximately half of the patients with carcinoma of the thyroid fall into this group.[56] According to the investigators, about 25 per cent of this group may be expected to concentrate the radioactive iodine. The alveolar and follicular carcinomas, which are much more malignant than the papillary type, are more readily able to concentrate the radioactive isotope. Three-quarters of this group took up I_{131}. Five of the 12 patients with solid carcinomas showed concentration of the radioactive iodine. Three of 9 patients with Hurthle cell carcinoma showed very minimal concentration

while no radioactive iodine was taken up at all by the giant and spindle cell or by the anaplastic carcinoma.

It would appear therefore from this study that alveolar and follicular solid and papillary carcinomas of the thyroid are the ones most readily able to concentrate radioactive iodine.

Spontaneous Creatinuria and the Creatine Tolerance Test.—Shaffer in 1908[57] was perhaps the first to describe abnormalities in creatine and creatinine metabolism in Graves' disease. He reported the occurrence of a significant creatinuria with a concomitant decrease in the urinary creatinine excretion in patients with this illness. With clinical improvement the creatinuria became progressively less. Some two decades later Palmer, Sloan and Carson[58] showed that the creatinuria of exophthalmic goiter disappeared both with the administration of iodine and with subtotal thyroidectomy. Kepler and Boothby[59] studied the spontaneous urinary creatine excretion in 145 patients with hyperthyroidism and in 274 instances of non-thyroid disease. Of the patients with hyperthyroidism 115 were instances of exophthalmic goiter and 30 were cases of adenomatous goiter with hyperthyroidism. Eighty-nine or 61 per cent of the patients with hyperthyroidism manifested a significant creatinuria. The incidence of positive results was approximately the same for both the patients with exophthalmic goiter and those with adenomatous goiter. Of the 274 controls definite amounts of creatine in the urine were found in 14 per cent of the women. An additional 9 per cent of the women showed a slight creatinuria. None of the male controls manifested definite creatinuria, although 9 per cent showed minimal amounts in the urine.

The absence of spontaneous creatinuria is characteristic of adult myxedema.[60–63] This observation is not particularly diagnostic since under normal circumstances, except for the occasional creatinuria observed in females, creatine does not appear in the urine in this age group. In children creatinuria may normally occur and its absence raises the suspicion of hypothyroidism. However, according to Wilkins and Fleischmann[67] creatine excretion is generally within the normal range in cretinism and juvenile myxedema, being of the order of 0 to 3.8 mgm. per kilogram of body weight as compared to values of 0.6 to 7.8 mgm. per kilogram in unaffected children. In both children and adults with myxedema the administration of thyroid extract results in a relatively prompt creatinuria which even precedes an increase in the basal metabolic rate or other evidences of improvement.[63]

It is evident from these studies, therefore, that the thyroid plays a significant role in creatine metabolism. The fact that creatinuria may occur in a variety of pathologic states, particularly those in which muscle mass and muscle function are involved, emphasizes the close relationship existing between creatine metabolism and muscle function. Creatine is methyl guanidine acetic acid and is synthesized from proteins, particularly the amino acids glycine, arginine, choline and methionine.[64] Approximately 98 per cent of the creatine is present in muscle and the remainder is found in the brain. More than half of the creatine in the muscle is present in combination with phosphoric acid as phosphocreatine, while approximately 20 to 40 per cent is available in the muscle in the free form.[65,66] Phospho

creatine is intimately concerned in the regeneration of adenosine triphosphate. The energy resulting from the dephosphorylation of the latter is believed to be involved in the contractile phenomenon of muscle.[64] The plasma content of creatine is very low, and under normal circumstances such low plasma concentration permits complete or almost complete resorption of creatine from the glomerular filtrate by the renal tubule. In normal adults, therefore, creatine is either entirely absent from the urine or present in quantities of less than 40 mgm. per twenty-four hours. In women during menstruation or gestation or lactation, and in both men and women during starvation or following high protein diets, there may be a considerable increase in the urinary excretion of this substance.

The end product of creatine metabolism is creatinine, this being an anhydride of creatine formed through the loss of one molecule of water. The conversion of creatine to creatinine occurs at a relatively constant rate. The daily amount of creatinine excreted in the urine in adults normally varies from 0.5 to 2.0 grams. This is quite constant, and because of its constancy this determination is often used to check the accuracy of the twenty-four hour urine volume. Creatinine, therefore, represents a waste product of creatine metabolism. The oral ingestion of creatinine results in its almost quantitative excretion in the urine, while more than 70 per cent of ingested creatine is retained by the normal adult.

In 1935 Richardson and Shorr[68] suggested the creatine tolerance test as an aid in the diagnosis of the more atypical instances of Graves' disease. The object of the procedure was to tax the creatine storing capacities of the muscles, a function which is impaired in hyperthyroidism. According to Shorr, evidence of a defect in the metabolism of creatine is indicated by: 1, a spontaneous daily creatinuria above 50 to 60 mgm. in twenty-four hours; 2, a retention of less than 70 per cent of the ingested creatine; and 3, a low daily output of creatinine per kilogram of body weight. The test *is performed as follows. The patient is placed on a creatine-free diet for* four days. Such a diet must contain *no* fowl, fish, meat or meat products, cocoa or chocolate. A twenty-four hour urine specimen is collected on the third day for the determination of the spontaneous creatine and creatinine output. On the fourth day the patient is given 1.32 grams of creatine hydrate dissolved in 180 cc. of water, and the urine is again collected for twenty-four hours and analyzed for creatine and creatinine. In making the calculations it should be remembered that the 1.32 grams of creatine hydrate is equivalent to only 1.0 gram of creatine expressed as creatinine. This is due to the loss of one molecule of water as water of hydration and another molecule of water is lost in the conversion of creatine to creatinine.

In patients with Graves' disease one or more of the indices mentioned above will be abnormal. Shorr and Richardson[69] employed the creatine tolerance test in several hundred patients with Graves' disease and found very few in which one or the other index was not impaired. This impairment in the retention of creatine in thyrotoxicosis was subsequently confirmed by other investigators,[70, 71, 72] and either a spontaneous creatinuria or a decrease in the retention of ingested creatine does indeed occur in a high percentage of patients with hyperthyroidism. Furthermore, as Shorr[69] has emphasized, the specificity of the test in Graves' disease is further

heightened by the disappearance of the spontaneous creatinuria and an increase in the retention of ingested creatine following the administration of iodine. Sohval, King and Reiner[71] have reported on the use of the creatine tolerance test in patients with Graves' disease and in 42 instances of neurocirculatory asthenia and 7 patients with the menopausal syndrome. A considerable spontaneous creatinuria occurred in 16 patients of this group of 49, and a decreased creatine tolerance was observed in 18 patients. Either a spontaneous creatinuria or a decreased creatine tolerance was noted in 27 patients, more than half of the group investigated. These investigators concluded that the usefulness of the test was limited in identifying borderline cases of hyperthyroidism.

In using the creatine tolerance test or the spontaneous creatinuria as an index of hyperthyroidism, certain pitfalls must be borne in mind. A spontaneous creatinuria frequently occurs in primary muscular disease, such as the various muscular dystrophies and in muscular atrophy. A spontaneous increase in the urinary excretion of creatine alone occurs in instances of muscular wasting secondary to central nervous system disease, such as poliomyelitis. Disturbances in creatine-creatinine metabolism are encountered in a variety of nonspecific pathologic states such as fever, acidosis and starvation. Finally, the ingestion of iodides either for therapeutic purposes or its innocent use in the form of iodized salts will inhibit the urinary excretion of creatine and increase the retention of orally ingested creatine in hyperthyroidism.

Magnesium Partition Studies.—We found[73,74] that in hyperthyroidism there occurred a considerable increase in the percentage of bound magnesium in the serum. Whereas in normal individuals the percentage of bound magnesium varied from 10 to 20 per cent, in patients with Graves' disease this fraction was often in excess of 25 per cent. The increase in the percentage of bound magnesium was not associated with any changes in the serum concentration of total magnesium but rather occurred at the expense of the diffusible fraction. In patients with myxedema, in contrast to the results observed in Graves' disease, all or almost all of the circulating serum magnesium was in the ionized form. Serum magnesium partition studies were reported by our group[74] in 50 patients with proven hyperthyroidism and in 7 patients with myxedema. In 6 of the patients with hyperthyroidism, the percentage of bound serum magnesium fell within the normal range level, that is, 20 per cent or less. In 9 additional patients the results were borderline, while in 35 cases there was a definite increase in the non-diffusible magnesium fraction. The total serum magnesium was essentially within the normal range level in the entire group. Following the administration of Lugol's solution, the elevated serum bound magnesium tended to return to normal levels. A further decrease in the bound fraction followed subtotal thyroidectomy.

In the patients with myxedema as well as in totally thyroidectomized dogs, the percentage of bound magnesium is extremely low and generally all of the circulating magnesium is in the diffusible state.[74] Following the administration of thyroxin or thyroid extract to the patients with myxedema and to the totally thyroidectomized dogs, there occurred an increase in the serum bound magnesium to approximately normal levels. The

administration of thyroxin to intact dogs will not affect this value but injections of thyrotropic hormone to such animals will cause an appreciable increase in the percentage of bound magnesium [75]

Dine and Lavietes [6] subsequently confirmed these results, both in patients *with hyperthyroidism and in instances of myxedema* Cope and Wolff [77] on the other hand failed to corroborate them The technic for the determination of magnesium partition is too difficult and the results too uncertain at present to permit of its routine use in hyperthyroidism *However the fact that the bound magnesium fraction is elevated in thyrotoxic states* and reduced in myxedema is of interest in that it establishes a possible relationship between this ion and thyroid function

The Relation Between the Circulation Time and Thyroid Function.—*Blumgart*[78] *has emphasized the close interrelation existing between the* velocity of blood flow particularly through the lungs and the basal metabolic rate In 1930 Blumgart Gargill, and Gilligan[79, 80] reported on vital capacity and circulatory studies in patients with thyrotoxicosis and in patients with myxedema In 5 of 9 cases with hyperthyroidism in the absence of any evidence of circulatory failure there occurred a decrease in the vital capacity of the lungs This confirmed the observations previously reported by Rabinowitch [81] The decrease however bore no particular relationship to the degree of elevation of the basal metabolic rate However subtotal thyroidectomy was generally followed by some increase in vital capacity Most marked changes were observed in the circulation time The velocity of blood flow was strikingly increased in the patients with hyperthyroidism The circulation time from the arm to the heart showed considerable variations although in most patients it was definitely reduced but the increase in the velocity of the blood flow through the lungs was a constant feature and was closely related to the elevation in the basal metabolic rate With the decrease in the basal metabolic rate which follower the administration of iodine there occurred a proportionate increase in the circulation time In patients with both thyrotoxicosis and cardiovascular disease the velocity of the pulmonary blood flow was still accelerated although not as markedly as that observed in the non-cardiovascular group with similar elevations in the basal metabolic rate

In myxedema even more so than in hyperthyroidism the vital capacity of the lungs is strikingly diminished in the absence of any evidence of congestive failure [82, 83] It is assumed in hyperthyroidism that the explanation of this phenomenon is the marked vasodilatation which occurs in this disease with a resultant encroachment on the pulmonary bed [78] This explanation however does not obtain in myxedema and the reason or reasons for the decrease remains obscure There is no close proportionate relationship between the degree of diminution in vital capacity and the degree of lowering of the basal metabolic rate Furthermore no significant change is apparent after therapy with thyroid extract [78] The velocity of blood flow is markedly reduced being the antithesis of that observed in hyperthyroidism As with the latter illness marked variations are observed in the arm to heart circulation time but the pulmonary circulation time is consistently slowed and corresponds to the degree of reduction of the basal metabolic rate [8, 80] After suitable treatment with thyroid extract there

occurs an increase in the basal metabolic rate and a parallel decrease in the circulation time.

Clinically, the measurement of the arm-to-tongue circulation time is of value in the confirmatory diagnosis of hyperthyroidism and to a lesser extent that of myxedema. In frank overt thyrotoxicosis the circulation time is almost always reduced, but in borderline instances and in the presence of congestive failure this finding is less constant and reliable. The presence of hyperthyroidism should be suspected in patients with congestive failure in whom the circulation time is not adequately prolonged.

The arm-to-lung circulation time measures the integrity of the venous side of the systemic circulation and the right heart and is in general half the saccharine time. Hitzig[84] suggested the use of ether for the measurement of the circulation time from the antecubital veins to the pulmonary capillaries. The technic consists of the injection of 5 minims of ether and 5 minims of normal saline into the antecubital vein and the length of time that it takes for the ether to become evident on the breath is noted. Baer[85] used the ether time in 169 normal individuals and found that the arm-to-lung time varied from three to nine seconds with an average of 5.8 seconds. The arm-to-tongue time varied in normal individuals from ten to fifteen seconds. Saccharine, decholin or sodium or calcium gluconate may be used to measure the arm-to-tongue time, which reflects the total heart efficiency. For this purpose 5 cc. of a 20 per cent solution of decholin, or 2.5 grams of saccharine dissolved in 2 cc. of water, or 5 cc. of a 10 per cent solution of calcium gluconate is injected into the antecubital vein. Decholin perhaps provides the sharpest end point, characterized by a bitter taste in the tongue readily perceived by all patients. Saccharine produces a sweet taste also readily recognized. However, the saccharine method is somewhat more cumbersome to perform since it involves heating the solution and permitting it to cool before injection. The end point with calcium gluconate is characterized by a warm sensation in the mouth. It must be emphasized that with all presently available methods for measuring circulation time the subjective factor dealing with the patient's perceptiveness plays some role.

When the ether time is subtracted from the total circulation time, the result reflects the velocity of blood flow through the lungs. Although the latter, according to Blumgart,[78] is most consistently influenced by changes in the basal metabolic rate, the available reports deal with the total circulation time in hyperthyroidism. Tarr, Oppenheimer and Sager[86] studied the total circulation time employing sodium dehydrocholate in 78 patients with proven hyperthyroidism. Ten patients in this group had evidence of congestive failure. In the 68 patients without congestive failure, the average circulation time was nine seconds with a range which varied from six and one-half to twelve seconds. In the patients with congestive failure, the range was wider, varying from six and one-half to nineteen seconds with an average of thirteen seconds. Of the 68 patients with hyperthyroidism without congestive failure, in 19 the circulation time was ten seconds or more.

These results are typical of those generally obtained when the arm-to-tongue time is measured. Where the thyrotoxicosis is overt, easily re-

cognizable clinically and uncomplicated by congestive failure the total *circulation time is most apt to be rapid* But the results are less consistent in the less well-defined instances and particularly in those patients with associated congestive failure An accelerated circulation time will *occur in fever and in beri beri heart in the absence of thyrotoxicosis*

Therapeutic Trial with Lugol s Solution as a Test for Hyperthyroidism — Untreated patients with thyrotoxicosis will show a dramatic response to *iodine Within ten to twenty-one days there will occur a considerable de*crease in the basal metabolic rate a slowing of the pulse an appreciable gain in weight and a marked improvement in the subjective symptoms *This response to iodine which occurs to varying degrees in the untreated* patient is often used as a test for the diagnosis of hyperthyroidism The advantage of this procedure lies in the fact that it requires no laboratory facilities other than perhaps the means of performing a basal metabolic determination Its disadvantages are that it takes ten to twenty-one days to determine the result which at best is crude and qualitative It is influenced by the previous ingestion of iodine and with the almost universal use of iodized salt this may be an important factor Finally despite all the safeguards subjective factors may considerably influence the results Even more so than with the other tests of thyroid function the response in the borderline patient is equivocal However improvement in the cardiac status of a patient with unexplained congestive failure or recurrent auricular fibrillation following the administration of Lugol s solution for several days strongly suggests the presence of hyperthyroidism

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Chapter 24

INFLAMMATORY DISEASES OF THE THYROID GLAND

Acute Non-Suppurative and Acute Suppurative Thyroiditis; Subacute Thyroiditis; Specific Chronic Thyroiditis; Hashimoto's Struma; Riedel's Struma

THYROIDITIS

Thyroiditis or inflammatory disease of the thyroid is relatively uncommon. Means[16] has stated that he has encountered it in 1 per cent of his total thyroid material. Thyroiditis may occur in a normal gland or in a gland previously the seat of disease. It may be acute, subacute or chronic and may be either suppurative or non-suppurative. Hashimoto's disease which is classified as a form of chronic thyroiditis has actually not been proven to be inflammatory in origin but may well represent a degenerative process.

Acute Thyroiditis.—The incidence of acute thyroiditis is about 0.5 per cent of thyroid disorders observed.[17,18] The disease reputedly occurs in young adults in the age group twenty to forty-nine, the extreme limits being eighteen months and seventy-seven years.[18] In our group of 12 patients with acute thyroiditis, observed only recently, 8 occurred in individuals over forty years of age. Not infrequently acute thyroiditis occurs in a goitrous gland. However, the current belief is that the finding is coincidental and depends on the endemicity of goiter in the region of the clinic. Only rarely, however, is hyperthyroidism complicated by this disease. The disorder occurs considerably more frequently in females than in males; in the material observed in our hospital the ratio was of the order of 3 to 1.

Acute thyroiditis is probably of infectious origin. Infection may be brought to the thyroid in several ways: (1) by direct extension of some perithyroidal infection, (2) by traumatic invasion of the capsule, (3) by extension through a persistent thyroglossal duct, or (4) by the blood stream or lymphatics. This last is certainly the most frequent mode of thyroid infection. In general, upper respiratory infections appear to be by far the most commonly encountered precursors of acute thyroiditis, being noted in about 50 per cent.[5,9] However, acute thyroiditis has been reported to follow a host of infectious diseases such as rheumatic fever, measles, influenza, meningitis, diphtheria, typhoid and paratyphoid fever, malaria, trypanosomiasis, pneumococcal, streptococcal and staphylococcal infections, and mumps. In short, acute thyroiditis is almost invariably secondary to an infection elsewhere in the body. It has been frequently claimed that it is

due to a viral infection but as yet no substantial evidence for this has been produced

Acute thyroiditis is but rarely suppurative for the thyroid appears to possess a definite resistance to a local infection perhaps because of its great vascularity Roger and Garnier[19] found that the injection of staphylococci and typhoid bacilli into the thyroid arteries through the common carotid resulted in but little reaction in the thyroid The injection of streptococci diphtheria toxin tetanus toxin, pilocarpin and iodides however produced acute thyroiditis In similar studies by Cole and Womack[9] the injection of streptococci and staphylococci into the thyroid artery only rarely resulted in suppuration When suppuration does occur in man it is usually due to septic emboli

Inasmuch as acute thyroiditis is of relatively short duration and of a benign nature little opportunity is normally afforded for the study of its pathology This entity however, presents the anatomic changes noted in acute inflammation occurring elsewhere There is dilation of the capillaries with diapedesis or even hemorrhage Subsequently there is a diffuse leukocytic infiltration even into the alveolar epithelium and a diminution in the colloid content of the follicles The inflammation may then subside or localize If the inflammation localizes it may result in abscess formation and the amount of destruction will depend essentially on the organism and the resistance of the host Spread of the suppurative process to the adjacent portions of the neck may occur as a result of infiltration and rupture On the other hand if the inflammation subsides it may result in complete healing without residue or there may remain foci of lymphocytic infiltration

The Clinical Syndrome of Acute Non suppurative Thyroiditis — The onset of acute thyroiditis is characterized usually by malaise fever which rarely exceeds 102° F occasionally chills pain and swelling in the region of the thyroid and dysphagia In a severely edematous gland difficulty in breathing may be present but this is more common when suppuration occurs A dry nonproductive cough and a sense of pressure in the region of the thyroid or fullness of the neck are often noted Hoarseness may be present Frequently the pain radiates to the back and side of the neck and up to the ear At times the pain may be unilateral if the inflammatory lesion is one sided The head is held forward to relax the prethyroid musculature especially during deglutition Only rarely are symptoms of hyperthyroidism noted[5] In 1 of the patients of our group the basal metabolic rate was plus 41 per cent and associated with mild signs and symptoms of hyperthyroidism all of which disappeared with the subsidence of the thyroiditis The physical examination generally reveals a tender enlarged thyroid gland The enlargement may be diffuse and symmetrical or one sided The gland may be nodular and feel harder than normal and indurated Heat and redness and edema of the surrounding tissues are unusual Regional lymphadenopathy may be present Only rarely if the inflammation extends beyond the capsule does the thyroid not move with deglutition There is generally a moderate increase in the total white blood cell count, which usually does not exceed 12 000 to 16 000 per cubic millimeter, associated with an increase in the polymorphonuclear leukocytes and a shift to the left Involvement of the recurrent laryngeal nerve

with vocal cord paralysis is not observed in acute thyroiditis Although the basal metabolic rate is usually normal the uptake of radioactive iodine has been reported to be reduced [22]

The usual course of acute non suppurative thyroiditis is a benign one and the process may subside in two to four weeks with complete recovery However the acute process may become subacute and last many weeks or months Recurrent episodes of acute thyroiditis have been reported [18] The *diagnosis* is usually clear *Acute cellulitis* of the neck is differentiated by the wide spread signs of inflammation in the neck as opposed to signs localized to the region of the thyroid In addition cellulitis usually begins in the upper part of the neck *Hemorrhage* into a *thyroid cyst* may result in pain and swelling of the gland but the constitutional signs of thyroiditis are lacking Hemorrhage frequently is noted following exertion The pain is sudden and rapidly subsides The *treatment* of acute thyroiditis *consists of* the usual general measures employed in any acute inflammatory lesion rest in bed fluids and analgesics An ice collar or local heat may make the patient more comfortable The antibiotics such as penicillin or aureomycin may be employed although their use is not followed by any dramatic response More encouraging results recently have been reported following the use of propyl thiouracil [2] This drug results in rapid improvement with subsidence of fever and pain within two to three days The drug is administered daily in a dosage of 300 mgm and continued until clinical resolution is complete Crile and his coworkers[1] have employed roentgen therapy in the treatment of sub acute thyroiditis with a complete and prompt response A large number of their cases would fall into the category which we include here as acute thyroiditis It is apparent therefore that acute thyroiditis will subside spontaneously but may be cured more promptly with the administration of either propyl thiouracil or x ray therapy to the thyroid gland

Illustrative Case

A forty five year old man was admitted with complaints of sore throat and dysphagia of ten days duration For the past four days he had noted a low grade fever During this latter period he had had an aching sensation in the neck jaw and extending to the ears Because of increasing dysphagia he sought admission to the hospital

On physical examination there was noted a diffuse swelling of the thyroid to 2 to 3 times its normal size The gland was tense and extremely tender The remainder of the examination was essentially negative The laboratory studies revealed a white blood cell count of 14 850 per cubic millimeter with 70 per cent polymorphonuclear leukocytes The sedimentation time was accelerated to twenty-one minutes for 18 millimeters

Following x ray treatment to the thyroid gland the patient s temperature which had attained a maximum level of 101 F fell slowly The gland became softer the tenderness subsided and he was discharged asymptomatic on the twelfth hospital day

The Clinical Syndrome of Acute Suppurative Thyroiditis — Acute suppurative thyroiditis is far less frequent than the acute non suppurative form [6 12] It may be a complication of non suppurative thyroiditis and appears to result more frequently when thyroiditis occurs in a pre-existing nodular goiter The danger of suppurative thyroiditis is that extension

may occur into the deep spaces of the neck and rarely even rupture into the trachea or esophagus

The clinical signs and symptoms are similar to those of the acute non suppurative form but the systemic manifestations are usually more severe The picture may be that of sepsis associated with local thyroidal signs Swelling and inflammation of the surrounding soft tissues often ensues Pressure symptoms are more frequent and severe than in the non-suppurative syndrome Finally fluctuation may occur The introduction of the antibiotics has resulted in a decrease in the incidence of suppuration and has markedly improved the prognosis When the diagnosis of suppuration is made surgical drainage as well as continuation of antibiotic therapy is indicated Care must be exercised during the surgical approach to avoid dissemination of the infection Occasionally, because of the presence of multiple loculated abscesses which cannot be adequately drained, partial or even total thyroidectomy may be necessary to eradicate the infection Rarely, where the suppuration has been extensive, healing will be associated with the development of myxedema As a rule however the prognosis is good both as to life and as to the adequacy of thyroid function

Illustrative Case

This case observed at The Mount Sinai Hospital, was previously reported by Sallick [6]

A thirty year old woman was admitted to the hospital complaining of pain in the midline of her neck anteriorly swelling of the neck and fever to 103 F of six days duration Deglutition had become difficult Examination revealed an acutely ill woman A large firm tender non fluctuant mass occupied the isthmus and right lobe of the thyroid displacing the trachea to the left The white blood cell count was 18 000 per cmm with 84 per cent polymorphonuclear leukocytes The blood culture was negative

In spite of supportive therapy and the use of adequate amounts of sulfanilamide she failed to improve The temperature rose to 104 4 F and the pulse became more rapid The swelling increased in size but no fluctuation was noted Dyspnea and dysphagia became progressively more marked She developed chills and the temperature rose further to 106 4 F while the peripheral white blood cell count increased to 37 500 per cmm Slight fluctuation was now observed and the gland was aspirated Foul smelling pus was withdrawn The gland was immediately incised and drained of 2 ounces of foul thick, purulent material from the right lobe and isthmus Culture of the pus yielded streptococcus viridans and streptococcus hemolyticus In the blood culture taken just prior to operation streptococcus viridans was grown After the operation improvement was prompt and the patient was discharged cured on the eleventh postoperative day

Subacute Thyroiditis — A number of patients with a clinically acute onset of thyroiditis have symptoms which persist for a period of months Indeed Crile has grouped these patients together with those having a disease of shorter duration under the generic heading of subacute thyroiditis He believes that this group[1] exhibits the same disease as that described by de Quervain and Giordanengo [21] In 1936 these authors reported 8 cases of subacute and chronic thyroiditis tracing the various stages of acute to subacute, and finally to the chronic stage Crile has described 27 cases Fifteen of these were subjected to x ray therapy in 2 biopsies were performed prior to x ray treatment and the remaining 10 were operated upon

The examination of the excised thyroid tissue showed evidence of a diffuse subacute inflammatory process. Grossly the gland is diffusely enlarged in most instances but in approximately a third the process is of a localized character in one or both lobes. No adhesions to the surrounding tissues are generally observed. The gland is a grayish white in color, smooth, and of a fairly firm consistency. The cut section is generally avascular. On histologic examination fibrosis of a variable degree is noted. This fibrous tissue which is laid down in characteristic whorls may be hard, coarse and often hyalinized. There are foci of small follicles with reduced or absent colloid. Many of the acini exhibit evidences of degeneration and frequently a granular coagulum containing collections of histiocytes may be found in the lumina. The intima and media of the smaller arteries are thickened. Lymphocytes and polymorphonuclear leukocytes, as well as numerous giant cells are found scattered throughout the gland. The frequent appearance of tubercle-like formations gave rise to the name "pseudotuberculous" or "giant cell" thyroiditis. The giant cell formation is probably a foreign body response to the colloid extruded from the degenerating follicles. This is lent weight by the fact that macrophages are found ingesting this debris.

Subacute thyroiditis is probably a phase in the genesis of Riedel's struma.[13, 1] This is denied by Crile[1] but most investigators favor this view.

Clinically the symptomatology is like that of acute thyroiditis. The course however is milder and much more prolonged. The major complaints are generally those of pain and enlargement of the neck with slight to moderate fever. According to Schilling[15] the disease occurs chiefly during the third and fourth decades and is approximately 3 times as common in women as in men. The disease responds promptly and completely to x-ray treatment of the thyroid. Usually a total dose of 600 to 800 r is adequate to produce cure.[14] Thyroidectomy will also result in cure but this procedure is rarely indicated since x-ray therapy will produce such prompt and satisfactory effects. In 1 case in our group the administration of 300 mgm. of propyl thiouracil daily resulted in a prompt subsidence of the symptoms and cure of the disease.

Illustrative Case

A sixty-three-year-old woman was admitted to the hospital because of a lump in the left side of the neck of eight months' duration. She had also noted some pain at this site. In the few weeks prior to admission to the hospital she had become hoarse. The physical examination revealed a diffusely enlarged thyroid gland which was hard especially at the lower left pole where it was fixed to the surrounding tissues. The remainder of the examination was essentially negative.

The basal metabolic rate was −12 per cent. A profile study with I_{131} revealed a diffuse uptake of the radioactive iodine by the thyroid. The blood count was normal. Exploration and total thyroidectomy were performed. The thyroid gland was found to be diffusely nodular and extremely hard and partly adherent to the surrounding tissue. The pathologic report was that of subacute thyroiditis with focal areas of dense fibrosis compatible with a diagnosis of Riedel's struma. Postoperatively the patient developed myxedema which responded to the administration of thyroid extract.

Chronic Thyroiditis.—Chronic thyroiditis may be specific or nonspecific. The specific forms, such as are due to syphilis,[2] tuberculosis,[9] and actinomycosis, are rare. Of over 130 cases of tuberculous thyroiditis reported in the literature, only 17 instances of tuberculous abscess were proven by demonstration of the tubercle bacilli.[20] The clinical picture was reported to be that of a cystic swelling of the thyroid of several months' duration which on incision was found to contain thick pus. This material was positive for tubercle bacilli on culture or smear. The wounds usually healed slowly. In none did myxedema ensue. In 9 of these patients an extra-thyroidal tuberculous focus was demonstrable. Fourteen of the patients made uneventful recoveries and 2 died of miliary tuberculosis.

Apart from chronic suppurative thyroiditis, which is rare, nonspecific chronic thyroiditis may be divided into two large groups, *Riedel's struma* and *Hashimoto's disease*.[10, 14] The former, which is a fibrotic form of thyroiditis, is probably inflammatory in origin, whereas the latter is more likely not. In 1896 and again in 1910 Riedel described[3] a form of extreme fibrosis of the thyroid under the title of "Eisenharte Strumitis." In 1912 Hashimoto described[4] a diffuse enlargement of the thyroid resulting from lymphocytic infiltration and hyperplasia of the lymphoid follicles. Although Ewing believed that Hashimoto's disease was probably an early phase of Riedel's struma, the majority of subsequent observers felt that the two processes were unrelated.[3, 14, 6, 31] The evidence for this point of view is fourfold: 1. The fact that biopsies on the thyroid of patients with Hashimoto's disease repeated years apart failed to show any changes suggestive of Riedel's struma. 2. The age group of the former is older than that of the latter. 3. Hashimoto's disease occurs almost exclusively in females, while Riedel's struma not infrequently afflicts males. 4. Hashimoto's disease is a diffuse process, while in a third of the patients with Riedel's struma the disease may be localized to one portion of the gland.

Riedel's Struma (Chronic Fibrous or Ligneous Thyroiditis, Struma Fibrosa).—Riedel's struma, or struma fibrosa, is a disease characterized by marked fibrosis in the thyroid gland, with destruction of the parenchyma and extension of the fibrotic process to the adjacent tissues of the neck. Schilling has postulated quite convincingly that subacute thyroiditis, or pseudotubercular thyroiditis, or struma granulomatosa (de Quervain), is the earlier or more acute form that in the later stages is described as struma fibrosa (Riedel). Struma fibrosa occurs most commonly in the fourth or fifth decades of life. Of 90 cases collected by Lee,[10] 66 occurred between the ages of thirty and sixty years. Similarly, of 12 patients studied in our clinic, 10 were between the ages of thirty and sixty-five. Sixty to 70 per cent of the patients are females.

The pathogenesis of the process is not entirely clear. Schilling[16] has postulated that with the inflammatory destruction of the acini and the release of colloid, irritating substances spill over into the stroma of the thyroid gland. These substances, acting as foreign bodies, are broken down by proteolytic enzymes, resorbed, and the glandular tissue then heals with fibrous tissue formation. De Courcy[11] pointed out, however, that frequently there is a considerable degree of local perithyroiditis which results in periarteriolar fibrosis with subsequent thickening of the media and intima of

these vessels. This author suggested, therefore, that the fibrosis of the gland results from these vascular changes. In any event, because of the similarity in the pathologic characteristics and in the clinical picture between subacute thyroiditis and Riedel's struma, Schilling[15] has suggested that the latter disease represents the end stage of the former, in which extensive fibrosis occurs during the healing phase. Studies in our laboratory tend to support this point of view.

Grossly the gland in Riedel's struma is extremely hard and fixed to the surrounding tissues. In over two-thirds of the cases the gland is diffusely enlarged, smooth and avascular. Nodules are only rarely felt. In one third of the patients the disease is localized to one or the other lobe or the isthmus. It is cut only with difficulty. Microscopic study reveals hard, dense, hyalinized fibrous tissue. In the uninvolved areas the acini may be normal but are frequently compressed. In the involved areas the acini are absent. The normal acini are infiltrated with acute and chronic inflammatory cells, but in the late stages these cells are very few in number. Occasionally pseudogiant cells are seen. The arterioles are thickened and have a periarteriolar fibrotic cuff.

Clinically the most important symptoms are those of pressure, and often asphyxia seems imminent. Dysphagia is common. The patients' complaints are usually of one to two years' duration, although the goiter may have been present longer. They may or may not have experienced some pain of the type encountered in subacute thyroiditis. Nervous symptoms attendant on the difficulty in respiration are often present. No symptoms of myxedema are noted, although occasionally some degree of hypothyroidism may ultimately occur. Hoarseness, aphonia or stridor may be present as the result of infiltration of the recurrent laryngeal nerves.

On physical examination the gland is found to be hard and fixed. It is commonly tender to the touch. The regional nodes are but seldom enlarged. The basal metabolic rate and the serum precipitable iodine are usually normal, while the uptake of radioactive iodine is only infrequently reduced and generally normal.[33,34]

The diagnosis is based on the finding of a hard, fixed thyroid mass. It is important to differentiate Riedel's struma from carcinoma. Although the presence of hypothyroidism favors Riedel's struma and the presence *of lymphadenopathy favors carcinoma, biopsy must almost invariably be* resorted to.

The accepted mode of treatment consists of the removal of as much of the mass as is surgically feasible. Lahey[2] claims that removal of the anterior segment of the thyroid is sufficient to relieve the pressure symptoms. Crile maintains that excision of the central degenerating adenomatous core will result in cure.[1] If a great deal of the remaining active thyroid tissue is removed, myxedema may result. If this occurs, treatment with thyroid extract is indicated. Postoperatively about 25 per cent of the patients develop hypothyroidism.[35] It is wise to bear in mind that the surgical procedure in these patients is attended with a great deal of difficulty. *Consequently one must be cautious to avoid injury to the recurrent* laryngeal nerves and to the other adjacent neck structures. After operation the disorder tends to become dormant and inactive, and secondary

operations are but rarely required Because of the underlying pathology the end results of surgery in late struma fibrosa may be poor, but in the earlier forms the relief of the mechanical pressure symptoms is often prompt and permanent X ray treatment is generally without effect

Illustrative Case

A fifty-one year old French governess was admitted to the hospital complaining of swelling of the left side of the neck, pain and hoarseness of six weeks duration Thirty-eight years previously she had had a goiter which had receded on iodine therapy The physical examination revealed a firm irregular thyroid, with enlargement chiefly of the left lobe The gland was fairly well fixed to the surrounding tissues and was tender to the touch The temperature was normal The red and white blood cell counts were normal and the basal metabolic rate was plus 2 per cent At operation the isthmus and left lobe were found to be infiltrated and replaced by a hard mass of tissue which was resected In addition a nodule was removed from the right lobe The pathologic report of the hard mass was that of Riedel s struma while the nodule was found to be a colloid adenoma After operation the patient was well

Hashimoto s Struma (Chronic Lymphoid Thyroiditis, Struma Lymphomatosa) —Hashimoto s disease is a disorder which is found almost exclusively in females only 8 cases having been reported in males [8] It usually occurs in the fourth fifth and sixth decades of life, although it has been reported in a ten year old child and a seventy-eight year old patient Little is known about the genesis of this disorder Joll[2] concluded that it was neither inflammatory neoplastic nor degenerative in any way comparable with what is usually understood by such terms It is known, of course that lymphoid tissue is more frequent in the thyroid of normal patients past fifty and is but rarely seen in the thyroids of normal young adults [27] It has been suggested that Hashimoto s disease is a disorder occurring in later years as a reaction to the degeneration of thyroid tissue It has also been suggested that the disease is due to prolonged iodine ingestion [8] particularly in the presence of a vitamin deficient diet [9] Finally because of the frequent occurrence of evidence of mild hyperthyroidism during the early stage of Hashimoto s disease and the extensive lymphocytic infiltration of the thyroid gland so common in hyperthyroidism a causal relationship between the two processes has been advocated [8 30]

On pathologic examination the thyroid gland is diffusely enlarged and firm There are no adhesions to adjacent neck structures except for occasional thickening of the pretracheal fascia On its surface the gland is smooth and pink in color It may have a pseudolobular appearance Microscopically there is a diffuse and uniform acinar degeneration The epithelium is flattened and the nuclei are dark and eccentrically placed The acini shrink and tend to coalesce with the formation of pale degenerate acidophilic cells Colloid is quite scant Pseudo-giant cells are occasionally seen With the degeneration a fine wavy fibrous tissue is laid down in characteristic whorls but the tissue is unlike that seen in subacute thyroiditis or Riedel's struma There is a diffuse lymphocytic infiltration Numerous typical lymphatic follicles are observed Plasma cells may be seen but polymorphonuclear leukocytes are rarely found The vasculature is normal [8 15 6]

In Hashimoto's disease the major clinical manifestation is diffuse thyroid enlargement There is generally no pain or tenderness, but occasion-

ally there may be some symptoms due to pressure such as dyspnea, dysphagia, *hoarseness, cough or stridor*. *Evidences of hypothyroidism or myxedema* are frequently present. When the patient is originally seen she has generally had enlargement of the neck and some symptoms for many years. The gland, however, feels much less firm than is observed in Riedel's struma and is more regular in its enlargement. In many instances there is an antecedent history that suggests the possible presence of mild hyperthyroidism before the onset of Hashimoto's disease. Indeed in a small but definite percentage of cases the basal metabolic rate may be elevated at the time of examination and it has been suggested that mild hyperthyroidism is a feature of the early stages of this illness.[8] Most patients with Hashimoto's disease will eventually develop hypothyroidism or myxedema. Davison and Letton[6] have reported that 9 of their 28 patients showed evidences of myxedema. McClintock and Wright[14] as well as Joll[2] in a much larger series of patients found that 79 per cent and 65 per cent, respectively, developed either hypothyroidism or myxedema. That this development occurs only late in the disease is evidenced by the fact that both the uptake and the urinary excretion of I_{131} is generally quite within the normal range and only rarely within the range level observed in hypothyroidism.[22,24] In the few instances in which the serum protein bound iodine was determined the results were similar to those obtained with radioactive iodine.[24]

Treatment consists either of the use of *x* ray therapy to the neck or surgery. Subtotal or total thyroidectomy has been employed. The results with *x* ray therapy are entirely satisfactory. There generally occurs a rapid shrinkage of the gland and prompt relief of pressure symptoms if any are present. Such cures may be effected within two to three weeks after the beginning of treatment. Recurrences as a rule do not occur but the incidence of hypothyroidism and myxedema is greater where either roentgen therapy or surgery is employed than where no treatment is used. The recommended dosage for *x* ray treatment is 1200 to 1500 r to each side of the neck in divided doses of 100 to 200 r.[1,15] There are no published reports as yet on the use of radioactive iodine in the treatment of this disease. Since these glands are generally capable of taking up the radioactive isotope it is probable that this agent will be equally effective as a therapeutic measure.

In summary, then, it is apparent that *Riedel's struma* and *Hashimoto's disease* are not the early and late manifestations of the same disease process[4,5] nor are they different manifestations of the same disorder.[9] They are separate and distinct pathologic entities. The former is apparently of inflammatory and perhaps infectious origin. The genesis of the latter is obscure but it is probably some type of degeneration. It is important to differentiate both these diseases from carcinoma of the thyroid. Because of the technically difficult and hazardous procedure involved in removing a struma fibrosa and the undesirability and lack of necessity for resection of a struma lymphomatosa, resection of the thyroid should not be carried out in doubtful cases except after confirmation of a diagnosis of carcinoma by biopsy. Clinically carcinoma may be suspected by the irregularity of the thyroid and the presence of regional lymphadenopathy but certainty is afforded only by biopsy.

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In Hashimoto's disease the major clinical manifestation is diffuse thyroid enlargement. There is generally no pain or tenderness, but occasion

Chapter 25

HYPOTHYROIDISM

Cretinism, Juvenile and Adult Myxedema (Gull's Disease)

Hypothyroidism is the clinical state resulting from an inadequate production of thyroid hormone by the thyroid gland. The manifestations of this glandular hypofunction depend on the duration and severity of the deficiency and the age of onset. The extreme clinical picture is observed *in cretinism and myxedema, which are due to the failure of thyroid function* occurring either before or after birth.

Thyroidal failure may occur under the following circumstances: 1. When the thyroid gland is congenitally absent or following total thyroidectomy. 2. When the gland is the seat of an extensive inflammatory or *infiltrative process, such as occurs in chronic thyroiditis of a specific or* nonspecific character in Riedel's struma and in Hashimoto's disease. 3. Following therapeutic destruction of the gland, as with the excessive use of *x*-ray therapy and radioactive iodine. 4. In association with the use of goitrogenic agents such as the thiourea derivatives and thiocyanates. 5. *Much less frequently in chronic prolonged iodine deficiency states.* 6. *In* so-called idiopathic atrophy of the thyroid gland, and finally 7. Atrophy of the thyroid gland secondary to adenohypophyseal destruction with the resulting decrease or failure of secretion of the thyroid stimulating hormone. This last occurs in patients with chromophobe adenoma, craniopharyngioma and Simmonds' cachexia. The hypothyroidism which results from adenohypophyseal disease is referred to as *secondary hypothyroidism* in contrast to the primary character of the other causes of hypothyroidism enumerated.

Cretinism.—Great strides were made in the study of diseases of the thyroid by the investigations carried out during the nineteenth century on the etiology of goiter and cretinism. The association of cretinism and goiter had been known in Roman times. In 1850 Curling[35] published the first 2 autopsy reports of patients with sporadic cretinism in which he pointed out the absence of the thyroid gland and the clinical similarity of those patients to those with endemic cretinism. The reports of Fagge[41] on sporadic cretinism, of Gull[42] on adult myxedema, and of Ord, who in 1888 reported on the autopsy of a patient with myxedema, were followed by the epochal report of the London Myxedema Commission.[40] This committee, on the basis of these clinical findings and the experimental work of Schiff on the thyroidectomized animal[51] and Kocher's studies on thyroidectomy in the human,[166] concluded that destruction of the thyroid gland was responsible for the various conditions described as *myxedema sporadic* and *endemic cretinism* and *cachexia strumapriva*.

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Chapter 25

HYPOTHYROIDISM

Cretinism, Juvenile and Adult Myxedema (Gull's Disease)

Hypothyroidism is the clinical state resulting from an inadequate production of thyroid hormone by the thyroid gland. The manifestations of this glandular hypofunction depend on the duration and severity of the deficiency and the age of onset. The extreme clinical picture is observed in cretinism and myxedema, which are due to the failure of thyroid function occurring either before or after birth.

Thyroidal failure may occur under the following circumstances: 1. When the thyroid gland is congenitally absent or following total thyroidectomy. 2. When the gland is the seat of an extensive inflammatory or infiltrative process such as occurs in chronic thyroiditis of a specific or nonspecific character, in Riedel's struma and in Hashimoto's disease. 3. Following therapeutic destruction of the gland as with the excessive use of x-ray therapy and radioactive iodine. 4. In association with the use of goitrogenic agents such as the thiourea derivatives and thiocyanates. 5. Much less frequently in chronic prolonged iodine deficiency states. 6. In so-called idiopathic atrophy of the thyroid gland, and finally 7. Atrophy of the thyroid gland secondary to adenohypophyseal destruction with the resulting decrease or failure of secretion of the thyroid stimulating hormone. This last occurs in patients with chromophobe adenoma, craniopharyngioma and Simmonds' cachexia. The hypothyroidism which results from adenohypophyseal disease is referred to as *secondary hypothyroidism* in contrast to the primary character of the other causes of hypothyroidism enumerated.

Cretinism.—Great strides were made in the study of diseases of the thyroid by the investigations carried out during the nineteenth century on the etiology of goiter and cretinism. The association of cretinism and goiter had been known in Roman times. In 1850 Curling[15] published the first 2 autopsy reports of patients with sporadic cretinism in which he pointed out the absence of the thyroid gland and the clinical similarity of those patients to those with endemic cretinism. The reports of Fagge[11] on sporadic cretinism, of Gull[12] on adult myxedema and of Ord who in 1858 reported on the autopsy of a patient with myxedema were followed by the epochal report of the London Myxedema Commission.[40] This committee, on the basis of these clinical findings and the experimental work of Schiff on the thyroidectomized animal[31] and Kocher's studies on thyroidectomy in the human[165] concluded that destruction of the thyroid gland was responsible for the various conditions described as *myxedema, sporadic* and *endemic cretinism* and *cachexia strumapriva*.

Cretinism is usually classified as *sporadic* or *endemic*, the former generally being due to congenital athyreosis. The endemic form is most often associated with goiter although some endemic cretins may exhibit athyreosis. When the onset of hypothyroidism can be established to have occurred after birth, the resultant clinical condition is referred to as *juvenile myxedema*. The child affected, however, may more closely resemble either a cretin or an adult with myxedema, depending on the age of onset of the disorder.

Of 292 cases of sporadic cretinism collected from the literature, 60 per cent were in females[11] and instances are reported in which more than 1 member of a family were afflicted.[17] This applies with even greater frequency to endemic cretinism. The familial frequency with which endemic cretinism is encountered is not at all astonishing in view of the fact that goiter is noted in 80 per cent of the mothers of these children. Although there are several rather extensive goiter areas in the United States, endemic cretinism is only infrequently encountered. Most instances of cretinism observed in this country are of the *sporadic* variety. Instances of *congenital goiter* with *cretinism* are recorded. The exact classification of this group is difficult, since they may be born to non goitrous parents living in non goitrous areas.

It is accepted today that the true picture of cretinism is that encountered in the patient with congenital athyreosis, or the typical sporadic cretin without goiter. In these individuals total failure of thyroid function has always been present, whereas in the endemic cretin with goiter the degree of thyroid insufficiency may vary from partial to almost complete. It is not yet known precisely when the thyroid of the fetus produces hormone for its own use. However, follicles appear in the eleventh to thirteenth week of fetal life[1,2] and colloid shortly thereafter.[5,7] Tracer studies with radioactive iodine have revealed that in the human fetus I_{131} is not collected by the thyroid until the fetus is fourteen and one half weeks old. The uptake of iodine in these studies was coincident with follicle formation and the appearance of colloid.[6] It may be presumed, therefore, that at this age physiologic activity of the thyroid begins and thyroid hormone is elaborated. Myxedematous mothers have been known to improve during pregnancy[182] and their offspring are normal.[24] There is no evidence at present to indicate that the placenta produces thyroid hormone, but there is some evidence to suggest the transmission of such hormone across the placental barrier.[182] The improvement noted in the myxedematous mother favors such an exchange. The fact that the skeletal development in the cretin with athyreosis is retarded at birth indicates, however, that only minimal transplacental transmission occurs.

Further light on the genesis of some types of cretinism is afforded by studies with the thiourea derivatives both in the rat and in the human. In the rat, which normally has a twenty two day period of gestation, thyroid follicles appear on the nineteenth day and iodine is capable of being concentrated in the gland.[8] The newborn litter of a rat to which thiouracil has been administered has minimal thyroid hyperplasia, although the gland contains no colloid and consists of solid cell masses. Postpartum, however, the follicles appear and colloid is seen within a few hours and fur-

ther development is normal unless these rats are fed thiouracil or nursed by thiouracil fed mothers. Under such circumstances, retarded development or cretinism is noted in association with thyroid hyperplasia.[4,150] These effects are prevented by the concomitant administration of thyroid hormone.[150]

In the pregnant human female with thyrotoxicosis, treatment with the thiourea derivatives does not exercise any effect on the infant provided the mother is maintained at euthyroid levels.[1,2,14] Spontaneous myxedema or cretinism in the mother is similarly without effect on the infant. However the fact that endemic goiter and endemic cretinism are so definitely related would suggest that thyroid deficiency in the mother due to prolonged iodine lack may result in a goitrous child probably with some degree of hypothyroidism. In endemic cretinism therefore the status of the maternal thyroid function undoubtedly plays a significant role. This is borne out by the fact that goiter is noted in 80 per cent of mothers of endemic cretinous children. No such relationship exists in sporadic cretinism.[12-8] A small minority of endemic cretins have athyreosis and in these the symptoms of thyroid deficiency have been known to be more pronounced than in cretins with goiter.[18,19] In this latter group there is apparently some thyroid function. Proof of this is further afforded by the fact that hyperthyroidism may supervene in an endemic cretin with a goiter but never in a cretin with athyreosis.[16,17] Physiologically the sporadic and endemic cretins without goiter fall into the same category—that represented by athyreosis. The cretins with goiter be they sporadic or endemic behave somewhat differently than this other group since the degree of hypothyroidism is less severe the goiter representing compensatory hyperplasia as the result of physiologic hypofunction.

Pathology of Cretinism.—In the infant with congenital athyreosis no thyroid tissue is found. Occasionally however small amounts of follicular tissue are present at the base of the tongue or at the normal site of the thyroid gland. In some cystic swellings that may be mistaken for colloid goiters but which are really distended ultimo-branchial bodies are apparent.[9] In the cretin with goiter thyroid tissue is present. There are focal areas of hypertrophy and of degeneration of the epithelium. The goiter commonly seen in endemic cretinism is usually a late development due to functional insufficiency of the gland.

Although typical changes of vacuolization of the basophils of the adenohypophysis have been reported in experimentally thyroidectomized animals the alterations noted in the untreated cretin are variable. In most instances the hypophysis is enlarged due to edema and the presence of cysts filled with a colloid like material. Occasionally, the hypophysis may be destroyed by such a cyst. In addition there are large numbers of chromophobe like cells apparently derived from the basophils. Both the eosinophils and the basophils are markedly reduced in number.[9] There is very little data concerning the histologic state of the adrenals in cretinism. Benda[9] was unable to find any abnormalities in the adrenals of 1 cretin examined at postmortem although Cramer has reported[10] a case in which he found retardation of involution of the fetal cortex. Without substitutive therapy the gonads of cretins usually fail to develop al-

though pregnancy has been reported.[110] The skin may show characteristic myxedematous changes. The heart is dilated and increased in size and in weight. The muscle is flabby and edematous. The bronchial mucosa may be thickened. The intestines are atonic and dilated, the kidneys and liver are reduced in size. The nervous system is markedly altered by congenital athyreosis. In general the picture is that of diffuse cerebral alterations resembling those of chronic anoxia, probably the result of the reduction of the cerebral metabolic processes. The brain may show agenesis or hypoplasia and the cord may be asymmetric. Severe neurologic complications are observed in 50 to 70 per cent of congenital cretins. Of 12 cretins studied in our hospital 2 had recurrent convulsive episodes and 2 were congenital spastics. When athyroidism develops later the neurologic changes are generally less marked, and the type of developmental arrest is influenced by the age of onset. In general thyroid deficiency in the young cretin will result in stunted brain development. It is for this reason that so many cretins are of low intelligence. Since the damage once sustained is at least in part permanent, they rarely attain their full hereditary mental potentialities.

The Clinical Manifestations of Cretinism.—It is rare today to encounter untreated adult cretins since almost invariably they have received some therapy. With treatment, a number of the abnormal characteristics disappear. Consequently, although young cretins are not seen too infrequently, the clinical manifestations of the untreated cretin can be garnered only from the older literature and from reports from mental institutions to which these unfortunates are ultimately sent.[9] The adult cretin is a dwarf, rarely being over 4 feet tall. He walks with a waddling, shuffling gait, in part due to the laxity of the hip joints and the bent legs. Curvature of the spine tends to shorten his erect height. The head is that of a normal sized individual but appears large when resting atop a dwarf. The hair is usually black,[9] wiry and strong. The orbits are large, the nose is broad and flat, the bony part being underdeveloped and the cartilaginous portion flabby. The cretin looks through a small palpebral fissure because of swollen, thick, puffy eyelids. The ears are large and flabby. The thick skin is pale and gray and of limited mobility due to the non pitting edema. The expression is dull and apathetic. All cretins resemble one another. The neck and trunk are short. In the supraclavicular areas there are often fatty pads or cystic masses. Although many female cretins have infantile breasts, in others they may become large and pendulous. An umbilical hernia is frequently present and the abdomen is pot shaped and protruding. Chronic constipation is common. The urinary output is small and may contain traces of albumin. Sexual infantilism is usual, but finally maturation may ensue and scanty pubic and axillary hair appear. The upper and lower extremities, as well as the fingers and toes, are short and broad. The nails are brittle. The body temperature is reduced 1° to 2° F and heat is well tolerated. The pulse may be slow but this is not invariable. The heart is enlarged, the sounds are feeble, and the blood pressure is often low.

The untreated cretin will not learn to speak. The motions are slow and awkward and the mentality is low. The menses are usually delayed but may

occur In addition it has been noted that abnormal neurologic signs such as hyperactive reflexes rigidity ataxia tremors deafness and deaf-mutism are often present

While these findings are of interest it is of considerable importance to recognize the early signs of cretinism in order that therapy be instituted promptly

Thus at birth the cretin may appear to be quite normal Usually he is of average length although somewhat heavy The child is quiet and slow and feeds poorly As time goes on the failure of normal development becomes more readily apparent The head is large and there is a wide open anterior fontanelle and frontal suture The nose is broad flat and depressed The cheek bones are prominent The palpebral fissures are horizontal and narrow due to the thickened heavy lids The skin is dry scaly and gray white The abdomen and umbilicus are protuberant Constipation is a very early manifestation The tongue is enlarged and thick The child fails to gain weight and growth remains at a standstill This results from the failure of the appearance of ossification centers Dentition is retarded As soon as the diagnosis is suspected *x* rays of the pelvis legs and skull are indicated since retardation of the ossification centers may be recognized even at birth

Legend for Figs 64 to 80

Figs 64 to 80 —Normal Osseous Development for Age as Shown by Roentgenograms of the Hands (Roentgenograms illustrating osseous development reproduced through courtesy of Dr L H Watson of Parke Davis & Company and Dr E R Witwer Attending Roentgenologist Children s Hospital Detroit Mich)



Fig 64



Fig 65



Fig 66

Fig 64 —At birth The carpal bones are cartilaginous but in an occasional case the capitate and hamate may just be visible The primary centers for the metacarpals and phalanges are well ossified but the epiphyses are absent

Fig 65 —Age one year Two carpals the capitate and hamate are present The osseous centers for the carpal bones appear at the rate of approximately one each year

Fig 66 —Age two years The lower epiphysis of the radius is present





Fig 67 Fig 68

Fig 67 —Age three years The triangularis can be seen and the epiphyses of the metacarpals and phalanges have appeared

Fig 68 —Age four years The lunate or fourth carpal bone is present and osseous development has advanced





Fig 69 Fig 70

Fig 69 —Age five years The trapezium or fifth carpal bone has appeared

Fig 70 —Age six years The scaphoid and the trapezoid (carpal bones) are present and the lower epiphysis of the *ulna may appear*

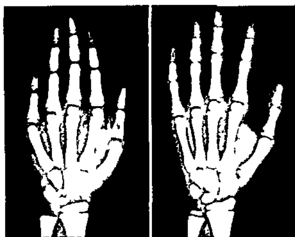


FIG 71 FIG 72

FIG 71 —Age seven years The bones of the hands and wrists show further development lower epiphysis of ulna may be present

FIG 72 —Age eight years. The lower epiphysis of the ulna is present Osseous development continues

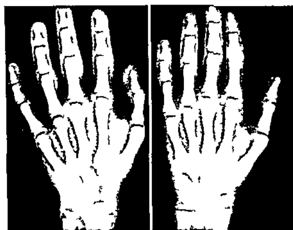


FIG 73 FIG 74

FIG 73 —Age nine years The pisiform may appear (Nine to eleven years)

FIG 74 —Age ten years Osseous development continues



Fig 75

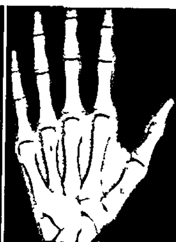


Fig 76

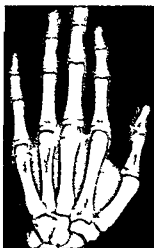


Fig 77

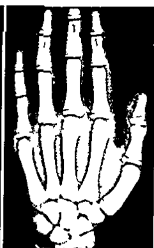


Fig 78

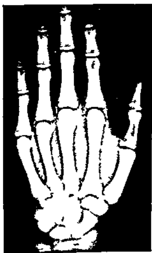


Fig 79



Fig 80

Legends at foot of page 77

In general cretins with goiter are not as deficient in thyroid hormone as are those with athyreosis Consequently, the skeletal and mental retardation is not as marked in the former as in the latter group [9 18 19] It is quite possible that in endemic cretins the increased metabolic needs of growth as the child becomes older may intensify an already existing thyroid insufficiency and result in further enlargement of the thyroid gland

The Diagnosis of Cretinism —The most important aid for the early diagnosis of cretinism is provided by the x ray whereby delayed ossification centers may be demonstrated early in life In the normal child at birth the lower end of the femur shows an ossification center At six months the centers for the head of the femur the capitate and hamate are present At one year of age the distal center of the epiphysis of the radius is evident in 90 per cent of normal babies

Appearance and Union of Bone Centers

These Tables have been revised from those of Engelbach and McMahon Camp and Cilley and E C Hodges

Years

1 Coracoid process scapula
   Head of humerus (six to seven months)
   Capitate and hamate
   Head of femur
   Upper epiphysis tibia (birth)
   Third cuneiform

2 Greater tubercle humerus
   Capitellum humerus
   Lower epiphysis radius
   Patella (two to three years)
   Lower epiphysis tibia
   Lower epiphysis fibula
   First and second cuneiform (two to four years)

3 Os triangularis
   Heads of metacarpals
   Heads of phalanges hands
   Heads of metatarsals (three to seven years)

4 Lunate
   Greater trochanter femur
   Upper epiphysis fibula (three to four years)
   Navicular (tarsal)

Legends for Figures 75 to 80

Fig 75 – Age eleven years The pisiform is present completing appearance of all of the centers of ossification for the hands and wrists

Figs 76 to 79 —Ages twelve to fifteen years There is continued osseous development with massing of the carpals (Note anomalous development of the proximal end of the second metacarpal in Fig 77)

Fig 80 —Ages sixteen and seventeen years The carpals are fully developed and massed the phalangeal epiphyses have united (fourteen to sixteen years) and the epiphyses of the lower ends of the ulna and radius have closed

APPEARANCE AND UNION OF BONE CENTERS (*Continued*)

Years	
5 to 6	Union of head and tubercles of humerus Medial epicondyle humerus Upper epiphysis radius Greater multangular Lesser multangular (six to eight years) Navicular (carpal) (five to six years)
7	Lower epiphysis ulna Union of ischium and pubis Epiphysis calcaneus (seven to nine years)
9	Pisiform (nine to eleven years)
10	Olecranon ulna Trochlea humerus
11	Lateral epicondyle humerus (eleven to twelve years)
13	Lesser trochanter femur Olecranon—Female
14	Union of heads of metacarpals (fourteen to fifteen years) Epiphysis os calcis—Female
15	Acromion Inferior angle scapula Union of centers of scapula (fifteen to eighteen years) Sternal end clavicle (fifteen to eighteen years) Union of heads of phalanges hand Appearance of secondary centers os coxæ (*a*) Crest of ilium (fifteen to eighteen years) (*b*) Acetabulum (fifteen to sixteen years) Union of primary centers os coxæ External condyle humerus—Female Head of radius—Female Trochanters—Female Head of femur—Female Olecranon—Male
16	Union of Distal extremity humerus Olecarnon ulna Upper epiphysis radius Heads of metatarsals Heads of phalanges feet Epiphysis of phalanges and metacarpals—Female Epiphysis of phalanges and metatarsals—Female Epiphysis os calcis—Male
17	Union of Lower epiphysis radius Lesser trochanter femur Distal epiphysis of the tibia and fibula—Female External condyle humerus—Male Head of radius—Male Trochanters—Male Head of femur—Male

Years

18 Union of

- Head of humerus
- Greater trochanter femur
- Lower epiphysis tibia
- Distal epiphysis of radius and ulna—Female
- Greater tuberosity of humerus—Female
- Distal epiphysis of femur—Female
- Proximal epiphysis of the tibia and fibula—Female
- Epiphysis of phalanges and metacarpals—Male
- Epiphysis of phalanges and metatarsals—Male

18 to 20 Union of

- Lower epiphysis ulna
- Secondary centers os coxae (twenty to twenty five years)
- Lower epiphysis femur
- Upper epiphysis tibia
- Lower epiphysis fibula
- Upper epiphysis fibula
- Distal epiphysis of tibia and fibula—Male
- Distal epiphysis of radius and ulna—Male
- Head of humerus—Male
- Greater tuberosity of humerus—Male
- Distal epiphysis of femur—Male
- Proximal epiphysis of tibia and fibula—Male

22 to 25 Union of sternal end clavicle

Between the ages of five and twelve girls seem to run about one year ahead of the boys after fourteen about two years ahead

Areas to be Taken for Bone-Age Determinations

1 to 5
(1) Full figure divided on two films
(2) Hands and feet taken separately
(2) Lateral knee for patella

6
(1) Carpals and tarsals
(2) Shoulder
(3) Pelvis

7
(1) Pelvis
(2) Carpals

8
(1) Carpals
(2) Lateral foot

9
(1) Carpals
(2) Lateral foot

10
(1) Elbow (lateral anteroposterior)
(2) Lateral foot
(3) Hand (anteroposterior)

11
Films listed under ages ten and twelve years

12
(1) Elbow (lateral anteroposterior)
(2) Carpals

13
(1) Hip with half pelvis
(2) Anteroposterior elbow
(3) Anteroposterior hand

14
Films listed under ages thirteen and fifteen years

APPEARANCE AND UNION OF BONE CENTERS. (*Continued*)

Years	
5 to 6	Union of head and tubercles of humerus Medial epicondyle humerus Upper epiphysis radius Greater multangular Lesser multangular (six to eight years) Navicular (carpal) (five to six years)
7	Lower epiphysis ulna Union of ischium and pubis Epiphysis calcaneus (seven to nine years)
9	Pisiform (nine to eleven years)
10	Olecranon ulna Trochlea humerus
11	Lateral epicondyle humerus (eleven to twelve years)
13	Lesser trochanter femur Olecranon—Female
14	Union of heads of metacarpals (fourteen to fifteen years) Epiphysis os calcis—Female
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16	Union of *Distal extremity humerus* Olecarnon ulna Upper epiphysis radius Heads of metatarsals *Heads of phalanges feet* Epiphysis of phalanges and metacarpals—Female Epiphysis of phalanges and metatarsals—Female Epiphysis os calcis—Male
17	Union of Lower epiphysis radius Lesser trochanter femur Distal epiphysis of the tibia and fibula—Female External condyle *humerus—Male* Head of radius—Male Trochanters—Male Head of femur—Male

Years	
18	Union of Head of humerus Greater trochanter femur Lower epiphysis tibia Distal epiphysis of radius and ulna—Female Greater tuberosity of humerus—Female Distal epiphysis of femur—Female Proximal epiphysis of the tibia and fibula—Female Epiphysis of phalanges and metacarpals—Male Epiphysis of phalanges and metatarsals—Male
18 to 20	Union of Lower epiphysis ulna Secondary centers os coxae (twenty to twenty-five year) Lower epiphysis femur Upper epiphysis tibia Lower epiphysis fibula Upper epiphysis fibula Distal epiphysis of tibia and fibula—Male Distal epiphysis of radius and ulna—Male Head of humerus—Male Greater tuberosity of humerus—Male Distal epiphysis of femur—Male Proximal epiphysis of tibia and fibula—Male
22 to 25	Union of sternal end clavicle Between the ages of five and twelve girls seem to run about one year ahead of the boys after fourteen about two years ahead

Areas to be Taken for Bone Age Determinations

1 to 5	(1) Full figure divided on two films (2) Hands and feet taken separately (2) Lateral knee for patella
6	(1) Carpals and tarsals (2) Shoulder (3) Pelvis
7	(1) Pelvis (2) Carpals
8	(1) Carpals (2) Lateral foot
9	(1) Carpals (2) Lateral foot
10	(1) Elbow (lateral anteroposterior) (2) Lateral foot (3) Hand (anteroposterior)
11	Films listed under ages ten and twelve years
12	(1) Elbow (lateral anteroposterior) (2) Carpals
13	(1) Hip with half pelvis (2) Anteroposterior elbow (3) Anteroposterior hand
14	Films listed under ages thirteen and fifteen years

AREAS TO BE TAKEN FOR BONE AGE DETERMINATIONS (*Continued*)

15	(1) Clavicle (2) Scapula (3) Pelvis (half) (4) Lateral foot (5) Hand (6) Lateral elbow
16	Elbow (lateral anteroposterior)
17	Pelvis
18	(1) Carpals (2) Tarsals (3) Shoulder (4) Pelvis with hip-joint (5) Ankle (anteroposterior)
19	Films listed under ages eighteen and twenty years
20	(1) Carpal with wrist (2) Knees (anteroposterior) (3) Ankle (anteroposterior)
25	(1) Clavicle (2) Scapula (3) Pelvis (4) Knee

In cretins, in addition to the delay in the appearance of these ossification centers, the epiphyses may remain ununited even well into adulthood. Instances of open epiphyses in sexually mature patients with myxedema have been reported.[103] Rings in the femur and humerus are noted on the x-ray in the older untreated cretin. With thyroid therapy the appearance of the ossification centers is accelerated. This affords a means by which the dosage and the efficacy of the therapy may be evaluated. Further roentgen evidence of hypothyroidism is provided by the persistence of the suture lines of the skull, the delayed closure and thinness of the anterior fontanelle, and the presence of a disc between the clivus and sphenoid body. Frequently the sella turcica is enlarged.[9] Wilkins has pointed out the frequent occurrence of epiphyseal dysgenesis[35,37] in untreated hypothyroidism and cretinism. Although calcification of the epiphyses is considerably delayed, when it does take place it appears as multiple small irregular foci scattered over a considerable area of the cartilage instead of extending peripherally from a single focus in the center. In addition this investigator has noted that in hypothyroidism the skeletal ratio of the upper segment of the body to the lower segment is similar to that of a child younger than the known chronologic age of the patient. The ratio normally changes from 1.7 at birth to 1.2 at five years and 1 at ten years of age.[35,37] The dividing line between the two segments is the top of the symphysis pubis.

In addition to the x-ray findings, the determination of the protein bound iodine of the serum is of great aid in the early diagnosis of hypothyroidism and cretinism. Rarely in such instances does this value exceed 4.0 micrograms per cent, and it is frequently less than 2.0 micrograms per cent.[23] The determination of the uptake and the urinary excretion of radioactive

iodine is less satisfactory as a test of decreased thyroid function. Although athyreotic cretins will show either a total absence or a marked decrease in the uptake of I_{131}, the results obtained in the goitrous cretin and older hypothyroids are much more variable and indeed in the former may be considerably increased.[1,21] The determination of the basal metabolic rate is impractical in infants, but in older children and in adults is almost always decreased, generally to levels which vary from −25 to −40 per cent.

The serum cholesterol is often elevated but is just as often quite well within the normal range. The change in the serum cholesterol level following the administration and cessation of thyroid therapy is of greater value in the diagnosis of hypothyroidism than is the isolated determination. Following the administration of thyroid extract or thyroxin there occurs a fall in serum cholesterol. However, the withdrawal of the hormone may be followed by a prompt and marked increase in the level, not infrequently exceeding 100 mgm. per cent, and reaching levels above those noted before the institution of therapy.[1-5,6,7,8] Such behavior is most suggestive of hypothyroidism.

Creatine excretion is generally within the normal limits in cretinism and juvenile hypothyroidism, being of the order of 0 to 3.8 mgm. per kilogram of body weight as compared to values of 0.6 to 7.8 mgm. in unaffected children.[6,27] The creatinuria is increased following the institution of thyroid therapy. In cretins with athyreosis the administration of thyrotropic hormone fails to induce creatinuria, thus establishing the absence of thyroid tissue.[25] The serum alkaline phosphatase is often decreased and the serum carotene level increased.[29,154] The hemoglobin and red blood cell counts are moderately reduced, while the white blood cell count is usually normal.

Differential Diagnosis. — The most important differential diagnosis of cretinism is that from *mongolism*.[69] The latter is recognizable at birth. The head is brachycephalic and the orbits are small. The eyes have an upward and outward slant as compared to the horizontal eyes of the cretin. There is an epicanthal fold present at the inner angle of the eye in the mongolian idiot. The bridge of the nose is small and underdeveloped. The short hands usually exhibit an incurved fifth finger due to maldevelopment of the second phalanx of that finger. The first and second toes are widely separated. Muscle tone is poor, but constipation is uncommon. Multiple congenital anomalies of the heart and eyes are often present. Although ossification may be delayed, it is not as pronounced and lacks the dysgenetic features observed in the cretin. In mongolism the basal metabolic rate, the serum protein bound iodine and the serum cholesterol are all within the normal range. Fertility is almost invariably absent, the genitalia being small and sexual development markedly retarded. The distinction between cretinism and mongolism is an important one since the former will show improvement with proper substitution therapy. Whenever there is any question as to the diagnosis, a therapeutic trial with thyroid extract should be instituted.

Gargoylism (Hurler's disease, Lipochondrodystrophy) is superficially similar to cretinism in that it too is characterized by stunted growth, thickness and coarseness of the skin, and mental retardation. It is readily differentiated from the latter by a number of features. The liver and

spleen are enlarged The hand is claw like in appearance, with an in curvature of the fourth and fifth fingers and a marked increase in the breadth of the hand Corneal opacities are frequently noted In addition the x ray findings of the skeleton are of importance in establishing the diagnosis In gargoylism, the vertebral column is deformed because of the retrodisplacement of the second lumbar vertebra The shortening of the vertebral bodies is evident on sagittal projection The ribs are clubbed, the ulna and radius are thick and short, and the metacarpal bones are bottle shaped Other causes of shortness of stature are generally readily differentiated from cretinism *Chondrodystrophy* is associated with normal intellectual development and except for the shortness of stature, enlargement of the head and flattening of the bridge of the nose bears relatively little resemblance to cretinism *Rickets* results in delayed ossification but is otherwise quite easily identified *Pituitary dwarfism* may cause some confusion and its differentiation from athyreosis has been discussed in detail in the chapter on hypophyseal dwarfism p 135 Delay in bone growth and development may occur as a sequel to a number of chronic wasting illnesses in childhood but the picture of the underlying disease is usually evident

Treatment of Cretinism —As soon as the diagnosis is established, treatment with thyroid extract is promptly instituted In infants it is given in a dosage of 4 to 6 mgm a day and increased in amount until euthyroidism is established as evidenced by suitable clinical and laboratory studies In older children the dosage is $\frac{1}{4}$ to $\frac{1}{2}$ grain daily and if necessary increased to as much as 2 to 3 grains As the child grows older the daily thyroid requirement is increased This is the explanation for the fact that the manifestations of hypothyroidism in some cretins with goiter is not evidenced for quite some time after birth when the metabolic needs begin to exceed the amount elaborated by the underfunctioning thyroid Following the administration of specific therapy remarkable changes are noted within a few weeks The facies alter the child becomes alert and responsive and starts to feed well The pot belly disappears and the bowels move with regularity There is a spurt in growth and development The ossification centers appear rapidly and within a period of months the appearance of the child is that of his chronologic age If thyroid is administered early enough normal physical growth and development may be expected to take place The later therapy is started the less satisfactory the result The prognosis as to the mental development of the cretin is not quite so favorable No matter how early treatment is begun most cretins will remain below normal intelligence [30, 34, 167] In one series only 3 of 35 patients attained normal mental development [30, 34, 167] The need for thyroid hormone in the early stages of development of the brain probably explains this later defect Nervous tissue unlike most other tissues is sensitive to injury and will fail to recover completely Consequently however brief the period of hypothyroidism almost invariably some irreparable damage is incurred

Other evidences of neurologic disease are rarely improved with therapy Deafness however, may be ameliorated Normal sexual development and fertility may be expected following adequate treatment although even without treatment instances have been reported of cretins propagating

successfully It is possible that some of these represent examples of spontaneous recovery of thyroid function In the cretin with goiter, euthyroidism may occasionally ensue spontaneously, and indeed even hyperthyroidism has been noted to occur[17] The explanation for this may be that if the goiter is due to some interference with thyroid hormonal synthesis such as iodine lack or the ingestion of some unknown goitrogen, the elimination of this factor is followed by normal thyroid function

The administration of thyroid extract may not only reduce the size of the goiter by inhibiting thyrotropin secretion by the adenohypophysis but may also furnish a ready supply of iodine It must be borne in mind that the cretin with goiter in general has a lesser degree of hypothyroidism than the cretin with athyreosis Consequently, although the response to thyroid extract will be less dramatic since the original hypothyroidism is less severe the ultimate prognosis is better In these children thyroidectomy occasionally may be indicated for cosmetic reasons Such surgery however will frequently intensify the hypothyroidism and therefore should not be attempted until adequate treatment of the thyroid deficiency has been sustained for a prolonged period

The administration of iodine to the cretin with goiter may be attended with varying results It may relieve the symptoms of hypothyroidism by supplying the substance lacking in the synthesis of the hormone[18] On the other hand it may provoke myxedema by involuting a gland that has just managed by hypertrophy and hyperplasia to compensate for a defect in its ability to synthesize the thyroid hormone[18]

In general the average thyroid requirements of the individual are dependent upon the age of the patient During the first few months of life it may vary from 4 to 8 milligrams a day At the end of six months the daily requirement increases to $\frac{1}{4}$ to $\frac{1}{2}$ grain From three to nine years it varies from 1 to $1\frac{1}{2}$ grains and from 2 to 3 grains by the age of eighteen It is important to emphasize however that although it is safe to treat the young patient with cretinism with the dosage schedule outlined the adult with myxedema should be started with minimal amounts of thyroid extract and the daily requirement only gradually reached

Illustrative Cases

CASE I

A three year old child was admitted to the hospital because of retarded development She had been a full term baby but she had been on an irregular diet and at the age of one year had had rickets Her mother had noted that the child was retarded in her physical development She started to speak at one and one-half years walked at the age of three years and dentition was considerably delayed The physical examination revealed a child of short stature with a thick dull apathetic monkey like facies The hair was coarse and short The anterior fontanelle was still open and admitted one finger The posterior fontanelle was closed The legs were bowed the abdomen was protuberant and pot-bellied The tongue was large thick and protruding The thyroid gland was not palpable The laboratory examination revealed a hemoglobin of 58 per cent and a red blood cell count of 3 1 million The blood total cholesterol was 350 mgm per cent which represents a considerable ele

vation The bone age on x ray was that of a one year old child The child was started on 1 grain of thyroid extract daily and this was then increased to 2 grains a day With this therapy she improved rapidly The facies altered the pot belly disappeared and she became active and playful The serum cholesterol fell to 180 mgm per cent She was discharged on 2 grains of thyroid a day

Case II

A twenty five year old known cretin was admitted to the hospital because of increasing difficulty in walking loss of hair and thickness of facial features A diagnosis of cretinism had been made at the age of three months At that time he had had an umbilical hernia coarse hair a pot belly, and had appeared unusually apathetic and dull He was given 1/10 grain of thyroid extract a day and on this he developed satisfactorily both mentally and physically At the age of four years he had a bilateral otitis media Deafness was discovered at the age of six and he was therefore sent to a school for the hard of hearing Five and a half years prior to admission to the hospital he had stopped taking thyroid extract Since that time he had noted a gradual coarsening and falling out of his hair thickening of the facial features slowness of the muscular response and difficulty in walking Although the patient had had a spastic gait all his life it had become noticeably worse during the past two years

The physical examination revealed a well-developed adult male with thick coarse skin The hair was coarse and sparse and the lips were thick The tongue was enlarged and the uvula was edematous The thyroid gland was not palpable The blood pressure was 80 60 mm of mercury Both ear drums were scarred The blood hemoglobin was 70 per cent and the red blood cell count was 3 5 million per cubic millimeter The white blood cell count was normal The basal metabolic rate was −48 per cent The electrocardiogram showed a sinus bradycardia low voltage of the QRS complexe and low P and T waves in all lead The blood cholesterol was 502 mgm per cent The electroencephalogram was normal

The patient was given 2 grain of thyroid a day and on this regimen his symptoms improved markedly The blood cholesterol fell to 235 mgm per cent and the basal metabolic rate rose to −5 per cent

Juvenile Hypothyroidism — Juvenile hypothyroidism encompasses both the features noted in cretinism and those in adult myxedema The symptoms and signs will depend on the age of onset of the disorder As in cretinism the manifestations encountered in juvenile hypothyroidism are not only the result of the lowered metabolic rate but are equally a reflection of the adverse effect of the glandular lack on growth and development Previously many authors had grouped cretinism and juvenile myxedema together However the better prognosis to be expected with the later onset of the disease is adequate reason for separating the two groups Acquired juvenile hypothyroidism may result from trauma thyroidectomy or following infections particularly the contagious diseases of childhood It is important for theoretical purposes at least to differentiate it from congenital cretinism with goiter which occurs in regions of sporadic or endemic goiter in which hypothyroidism is precipitated some time after birth when the requirements for hormone exceed the ability of the thyroid to secrete it

The important clinical features of the syndrome are summarized in the following two tables adapted from Wilkins [36]

TABLE 26.—CLINICAL SIGNS IN JUVENILE MYXEDEMA (FROM WILKINS)

Structural Changes

- Skeleton
  - Height stunted
  - Skeletal proportion upper lower segment infantile
  - Naso-orbital development infantile
  - Osseous development retarded
  - Dental development retarded and defective
  - Epiphysial dysgenesis frequently present
- Other Structures
  - Brain development retarded
  - Skin variable
  - Hair variable
  - Subcutaneous tissue variable

Functional Changes

- Physical and mental torpor
- Peripheral circulation poor skin pale grayish cool
- Pulse rate slow and pulse pressure high
- Sweating variable
- Constipation
- Biochemical and metabolic changes

TABLE 27.—BIOCHEMICAL STUDIES (AFTER WILKINS)

	Hypothyroidism	*Euthyroidism (for comparison)*
Basal Metabolic Rate		
Surface Area Standard	−15 to −40%	−10 to −28% (obesity)
Height Standard	−14 to −33%	−15 to +40% (obesity)
Cholesterol—before treatment		
Range for Group	150–600 mgm %	100–300 mgm %
Spontaneous Fluctuations	200 mgm %	83 mgm %
Creatine—before treatment	0.0–3.8 mgm per kilo day	0.6–7.8 mgm per kilo day
Sensitivity to 1 mgm of Thyroxin		
Cholesterol Decrease	120–229 mgm %	0–6 mgm %
Average Duration of Effect	38 days	9 days
Withdrawal of Thyroid		
Cholesterol Increase	98–411 mgm %	10–64 mgm %
Effect of Thyrotropic Hormone on Output of Creatine	negative	positive or false negative
Serum Precipitable Iodine	<4.0 gamma %	4.0 to 8.0 gamma %
Serum Phosphatase	decreased	increased
Radioactive Iodine Uptake	decreased	normal
Urinary Excretion of Radioactive Iodine	often increased	normal

Treatment.—The therapy is based on the same principles which are employed in the treatment of the cretin and the adult with myxedema. The older the patient at the onset of the disease the more favorable the prognosis is for physical and mental development. Early therapy is of great value in permitting the patient to attain his maximum potentialities. In general

however the prognosis is better than in the cretin and may be as good as in the adult with myxedema

Adult Myxedema

Following the reports of Curling,[15] Fagge,[41] Ord,[4] and Gull,[43] and the Commission of the Clinical Society,[40] Murray[44] demonstrated that the signs and symptoms of adult myxedema could be favorably influenced by the administration of thyroid extract. As a result of these studies it became evident that myxedema could be controlled with this therapy and that the life expectancy of the patient need not be shortened and his efficiency not impaired if adequate treatment is employed. Recently Burgess reported an instance in which a patient with myxedema lived to the age of ninety-two having been on thyroid extract for fifty-two years.[14]

The clinical picture that was described in such graphic detail in the Commission's report is still the classical picture of myxedema. The recognition of the illness at this stage is no problem but only relatively infrequently do patients remain untreated long enough to present the full-blown syndrome.

Hypothyroidism or myxedema may be due to primary or secondary dysfunction of the thyroid gland. Primary myxedema occurs after total thyroidectomy following the administration of radioactive iodine in excessive dosage and after the ingestion of goitrogens. It may also occur as a result of diffuse destructive disease of the thyroid gland such as chronic thyroiditis, Hashimoto's disease and extensive tuberculous destruction of the gland. Idiopathic primary atrophy of the thyroid accounts for a considerable percentage of the adult patients with myxedema. Secondary hypofunction of the thyroid gland follows destructive lesions of the adenohypophysis. Chromophobe adenomas, craniopharyngiomas and atrophy of the adenohypophysis such as occurs in Sheehan's syndrome and in hypophyseal cachexia are the usual causes for secondary myxedema.

Pathology of Myxedema —Autopsy studies in patients with untreated myxedema are rare. Today the disease is readily recognized and most patients are promptly subjected to adequate therapy. Consequently the available pathologic studies are those reported in the older literature plus the few more recent cases.[40,45]

The thyroid gland in primary idiopathic myxedema shows a marked diminution in size and weight. The fibrotic atrophic thyroid contains only small remnants of the gland and it is infiltrated with chronic inflammatory cells. The acini and colloid have disappeared for the most part and lymphocytes and fibrous tissue predominate. Scattered throughout are some epithelial cells. The arteries show degenerative changes and narrowing.

Although thyroidectomy in the experimental animal is followed by vacuolization of the basophils of the adenohypophysis as well as enlargement of the pituitary, such changes are not always noted in adult myxedema. In the cretin edema and colloid formation in the adenohypophysis plus the appearance of "chromophobe-like" cells has been observed. In the hypophysis of the adult with primary myxedema due to atrophy of the thyroid

or following thyroidectomy, no constant histologic picture has been reported. Frequently, however, the hypophysis is noted to be enlarged and there is an increase in colloid [46, 47]

No recent studies on the histology of the adrenals in clinical untreated myxedema are available. According to the reports in the older literature where very inadequate technics were employed the adrenals are said to be normal. In the experimental animal the adrenal cortex is reported to be atrophic following the administration of thiouracil [50] Although rarely the parathyroids have been reported to be enlarged, usually no alteration is noted. Recently a case of the coexistence of myxedema and hyperparathyroidism was reported [1, 2] In cretinism and following experimental thyroidectomy the islands of Langerhans are said to be increased in number. This is not usually observed in adult myxedema [11] The gonads may be atrophic [40] The heart is dilated and the muscle wall thickened. This probably represents edematous infiltration of the muscle rather than true hypertrophy [46] Frequently a pericardial effusion is present but there is no evidence of pericarditis. There may be edema between or within the muscle fibers which may undergo degeneration, necrosis and replacement fibrosis [43, 44] A homogenous infiltration in the myocardium supposedly different from that occurring in the skin has been reported [54] The coronary arteries often show advanced arteriosclerosis [50] A polyserositis is frequently encountered and may be a predominant symptom [56] The skeletal muscles show lesions consisting of degeneration of the central portion of the sarcoplasm and the presence of vacuoles containing basophilic material [55] Identical changes may be noted in the visceral musculature as well as in the heart. Changes such as these have also been described in the aorta [45, 57] and resemble those of idiopathic cystic medial necrosis [58] The liver shares in the interstitial edema seen elsewhere. The bones in myxedema are more heavily calcified than is ordinarily observed [39] The brain shows considerable edema and in addition changes similar to those observed in cerebral arteriosclerosis or in arosemia. The skin is the site of the changes from which the disorder derives its name. Hyperkeratosis, irregular scattered epidermal atrophy with degenerative changes, edema of the corium and of the collagen fibers are noted. In addition there may be some sparse perivascular cellular infiltration. The characteristic finding is the presence of a mucinous staining material [60, 61] Recent studies would suggest that this substance is a mucoprotein containing hyaluronic acid [62]

Incidence —The incidence of myxedema is reported to vary from 0 0002 per cent to 0 08 per cent of hospital admissions. Most observers however report figures closer to the latter incidence [49, 63, 64] Over an eight year period at The Mount Sinai Hospital the incidence was 0 08 per cent of all hospital admissions which totalled approximately 120 000 over this period of time. The disorder is more common in females in a ratio of 4 1 [49, 63, 67, 68] The ratio in our series is slightly greater being 5 1. Although Thompson[63] claims the disorder is most common in the fourth, fifth and sixth decades of life, Burnstein found half of his cases to be less than forty years of age [65] and Kohlhas[67] found the average age in his series to be thirty four years. Our experience is similar to that of Thompson except that in addition we encountered myxedema frequently in the seventh decade. Means and

Richardson[184] found the largest group of cases in the fourth decade, with the age range varying from twenty to sixty years

Signs and Symptoms — The signs and symptoms of myxedema are gradual in onset The patient first notes fatigue and weakness and a curious intolerance to cold He becomes lethargic and is aware of increasing somnolence No amount of sleep however assuages either the somnolence or the fatigue The appetite is decreased, but despite this there may be a considerable gain in weight although this is by no means invariable *The mental faculties become impaired the memory poor* and the increasing dullness becomes progressively more apparent to the patient's friends and



Fig 81 —Note the apathetic appearance of the patient and the rough scaly pigmented skin

family The speech is thick slow and deliberate and the voice hoarse and low pitched *The eyes become puffy The skin and hair are dry* and coarse and the pubic axillary and head hair sparse The myxedematous swelling eventually envelopes the entire body and the face assumes the characteristic pallor and configuration A moderate secondary anemia is generally present In the female various menstrual abnormalities may occur Menorrhagia is perhaps most common but oligomenorrhea and even amenorrhea are often encountered The heart becomes enlarged and

evidence of cardiac insufficiency may ensue. Pericardial effusions and more rarely serous effusions of the pleura and peritoneum may be observed.

These signs and symptoms can be reversed with treatment. In the untreated patient, however, the clinical picture becomes progressively more marked until death results ten to fifteen years after the onset of the disease, due generally to intercurrent infections and to congestive heart failure.

Because thyroidal insufficiency results in a reduction of the metabolic activities of all the tissues in the body, the effects of myxedema or hypothyroidism are reflected in all the organs.

The Skin. — The skin is cold, dry and thickened. The coldness is due to several factors. The peripheral circulation is slowed and the vasculature is insulated from the skin by the mucinous infiltration. The decrease in metabolic activity, and therefore the decreased production of body heat, is associated with peripheral vasoconstriction in a compensatory effort to minimize further heat loss. The skin is dry for similar reasons in addition to the direct effects of the lowered metabolism on decreasing the activity of the sweat glands. The skin usually does not pit because of the firmness of the mucin in the subcutaneous tissues. This mucoid substance is probably a mucoprotein containing hyaluronic acid and may be pitted after the injection of the enzyme of hyaluronidase. Incised wounds or traumatic ulcerations heal slowly, since wound healing is delayed or prevented by the abnormalities in the connective tissue. The nails grow slowly and are thickened and brittle, and the surface is often ridged. The hair on the scalp and face is sparse and the eyebrows thin and scanty, particularly in the outer portions. There is a curious edema about the eyes, and the infiltration of the skin of the face renders it relatively immobile. The nose is broad and thick and the lips are swollen. In general, the skin of the face conveys a dry parchment appearance. The tongue is large, coarse and thick, and the uvula is edematous. The voice is indistinct and slow, and its pitch low and hoarse, probably due in part at least to alterations in the laryngeal submucosa. The extremities are large and swollen but the edema is non-pitting in type. The massiveness of the extremities is not associated with an increased thickness of the bony structure but is related to the extensive myxedematous infiltration of the subcutaneous tissue.

The Circulation. — Myxedema is associated with changes in cardiovascular function in approximately three-quarters of the patients. This observation has been repeatedly confirmed since the original report of Zondek.[9, 53, 1–80]

The peripheral vascular bed is greatly reduced and the peripheral blood flow diminished.[81] Indeed, the blood flow to the skin may be only 1.3 per cent of the cardiac output as compared to 4 per cent in the normal subject.[81] Capillary permeability is increased[82] and as a result the edema fluid is high in protein. This is particularly noted in the serosal effusions. The reduction in peripheral blood flow is associated with a decrease in the venous return and a reduction in cardiac output.[83] With adequate therapy the cardiac output in myxedema approximates a normal level. When therapy is discontinued, however, the output promptly falls and may be reduced by one-third. The low cardiac output reflects the low pulse rate and the decrease in stroke volume. The slowing down of all metabolic functions is

similarly reflected in the slowing of the velocity of blood flow, the arm to tongue circulation time frequently being prolonged.[77,83] The venous pressure is usually within the normal range, although increases have been reported.[9,82] The probabilities are that most instances which manifested increases in venous pressure were complicated by congestive failure. Although the circulating blood volume is diminished, the reduction in the metabolic functions are so considerable that this reduced blood volume is nevertheless sufficient to satisfy the needs of the tissues.[84] The increase in the arterio-venous oxygen difference serves as an accessory aid in ensuring adequate nutrition to the tissues despite the diminished vascular supply.[83] In addition, the oxygen requirement during effort seems to be less in the myxedematous patient than in the normal subject.[85] Hence, in effect, the "work efficiency" of the patient with myxedema is greater than that of the euthyroid individual. No constant changes in the blood pressure are noted in myxedema, although there is a tendency for the systolic, diastolic, and pulse pressures to be low. It has been claimed that following therapy, however, the incidence of hypertension is greater than in the general population.[86]

The premise that a reduction in the metabolic needs of the body results in a decreased burden on the heart led to the introduction of total surgical thyroidectomy in the treatment of angina pectoris.[88] Later the use of radioactive iodine replaced surgery for the therapeutic induction of myxedema.[87] The use of these measures has resulted in the amelioration of the anginal symptoms of some patients. On the other hand, the anginal syndrome is often associated with myxedema, probably the result of the severe generalized and coronary arteriosclerosis. In those patients with myxedema but without angina, the administration of thyroid extract may result in the development of angina pectoris concomitant with the rise in the basal metabolic rate.[90] This will also occur in the patients with angina pectoris in whom myxedema was induced for relief of the coronary pain. There are some instances in which angina associated with myxedema improves with thyroid therapy.[89,91] We have seen one such patient. Although the explanation for the improvement is not clear, it is possible that the improved cardiac efficiency may more than compensate for the increased cardiac load. There is probably an optimum dosage of thyroid therapy beyond which the increased metabolic demands may again tax the heart.

The heart in myxedema is usually enlarged.[5] This may not necessarily be obvious during the initial examination, but with the administration of thyroid extract it almost invariably becomes smaller. The enlargement may be due to interstitial edema, to pericardial effusion, to dilatation, or to a combination of several of these factors. When dilatation is present, it usually involves all the chambers. This is characteristic of the myxedema heart. The apical impulse is diffuse, rather flabby, and difficult to localize, in part because of the feeble contractions and in part because pericardial effusions, although generally small in amount, are so often present. The heart sounds are distant, muffled, and of poor quality.

The electrocardiogram is generally abnormal in this disease. There is a sinus bradycar[illegible] with low voltage in all complexes and flattening and even inversion [illegible]es and not infrequently reduction in amplitude of the

P wave. Other changes that are occasionally noted include a prolongation of the PR interval or a widened QRS phase. These alterations in conduction usually indicate myxedematous infiltration of either the bundle of His or one of the branch bundles. Those electrocardiographic changes which are directly due to myxedema of the heart are reversible after treatment with thyroid extract for several weeks. In those instances in which improvement fails to occur with specific therapy, the observable electrocardiographic changes are more likely due to actual myocardial damage resulting from the coronary sclerosis so often associated with myxedema. It is not clear as to what role the pericardial effusion plays in the electrocardiographic alterations observed in these patients.[94] Since pericarditis does not occur as part of the clinical picture of myxedema, ST segment changes are as a rule not noted. Their presence in patients with myxedema should arouse the suspicion of coronary artery disease.

In general, it may be stated that there are no electrocardiographic changes which are pathognomonic of myxedema. The presence of a bradycardia in association with a low voltage in all complexes should, however, suggest this diagnosis. The poor conductivity of the skin apparently plays no role in the electrocardiographic abnormalities, since White was able to obtain similar tracings with needle electrodes.[49] The ballistocardiograph is reported to be frequently abnormal in myxedema.[94]

Myxedema is sometimes accompanied by evidences of congestive failure. It is a moot point, however, as to whether myxedema alone is capable of producing sufficient cardiac change to result in decompensation. In 1925 Fahr[43] described gross congestive failure occurring in association with myxedema which failed to respond to digitalis but improved remarkably following the administration of thyroid extract. Several years later he described additional instances of this syndrome which responded either partially or completely to the thyroid hormone. The existence of this specific entity as described by Fahr is controversial and the controversy centers essentially about two points. The first deals with the question of whether these patients actually had heart failure. Edema, dyspnea, and serous collections of fluid occur as a result of myxedema *per se* even in the absence of heart failure and will respond well to thyroid hormone and not at all to digitalis. Changes in the size of the heart and electrocardiographic abnormalities, both responsive to thyroid extract, are frequently noted in myxedema, but of course cannot be used as actual evidence of congestive failure. Unfortunately, venous pressure determinations were not in routine use at the time and hence the diagnosis of heart failure was based on features which are of equivocal significance in this disease. Today, the fact that the protein content of the serous effusions observed in myxedema is high in contrast to that in heart failure, the presence usually of normal venous pressures, the decrease in circulating blood volume, and the failure to respond to mercurial diuretics as well as to digitalis suggest that the usual clinical phenomena observed are not on the basis of myocardial insufficiency.

This of course does not mean that patients with myxedema may not develop congestive failure, and indeed they often do. The second point deals with the possible presence of additional etiologic factors in those

patients who do manifest heart failure The frequency of coronary sclerosis and even hypertension in patients with myxedema lends considerable weight to the opinion that heart failure in this group is generally due to an additional factor which in itself may cause cardiac decompensation [5]

In any event it is wise to think of myxedema as a disease capable of producing certain cardiac changes and peripheral phenomena which are responsive to thyroid therapy These changes by themselves may not perhaps induce myocardial insufficiency, but if the cardiac reserve is further interfered with such as may occur with coronary artery disease and for a variety of other reasons actual congestive failure may more readily be precipitated

The Blood in Myxedema — Almost two-thirds of the patients with myxedema will show some degree of anemia [97] The type of anemia most frequently seen in this disease is a normocytic anemia Much less frequently a macrocytic anemia distinct from pernicious anemia is encountered and occasionally a hypochromic anemia is observed The macrocytic anemia occurs in both the spontaneous and the postoperative myxedema and is characterized by an increase in the mean corpuscular volume although the mean corpuscular hemoglobin concentration is essentially within normal limits [9, 98] In this type of anemia the red blood cell count is rarely less than 3.0 to 3.5 million per cubic millimeter or the hemoglobin below 60 to 70 per cent In contrast to true pernicious anemia bone marrow studies in these patients reveal a mildly hypoplastic marrow with a decrease in the number of nucleated red blood cells [99] In the peripheral blood there is little anisocytosis of the red cells and poikilocytosis is practically never observed The specific character of this anemia is attested to by the fact that it responds neither to liver nor to iron but will improve slowly with thyroid extract

Achlorhydria occurs in slightly over half the patients with myxedema and in this group anemia is generally more apt to occur The normocytic anemia will tend to disappear following improvement of the hypothyroidism The hypochromic anemia sometimes observed in these patients will respond well to the administration of iron In general all three types of anemias require thyroid extract either specifically for treatment or as an adjuvant to other anti anemic therapeutic measures such as iron Patients with hypothyroidism may develop true pernicious anemia Under such circumstances the two diseases are not causally related but may exist coincidentally in the same individual Pernicious anemia may be present in such patients either in the absence of or in conjunction with the specific anemia of hypothyroidism In the former case liver extract or vitamin B_{12} will correct the abnormality but in the latter instance thyroid extract must be used in addition [100]

The white blood cell count in myxedema presents no abnormalities The total count and the differential studies are well within the normal range

The Genital Tract —In both sexes libido is generally reduced and sterility may accompany the hypothyroid state although pregnancy has been reported in the untreated cretin and in the patient with myxedema [3, 4] Following treatment with thyroxin or thyroid extract fertility is improved

Menorrhagia and amenorrhea occur frequently in myxedema. It is essentially because of these observations that gynecologists empirically treat ill-defined menstrual disorders with thyroid extract.[134,135] It has been observed recently that the serum protein bound iodine rises during normal pregnancy and that a persistently low value is often associated with spontaneous abortions. Such abortions in patients with low serum protein bound iodine may be prevented by the use of thyroid extract.[111,112]

The Urinary Tract.—There is a reduction in the renal blood flow, glomerular filtration, and maximal tubular excretion of diodrast (Tm_D) in myxedema.[101] The urea clearance is similarly reduced.[107,168] Following treatment with thyroid extract restoration towards normal occurs. The renal blood flow rises in proportion to the basal metabolic rate, although the glomerular filtration is increased to a far greater proportion, indicating vasodilatation of the glomerular afferent vessels. A disproportionate increase is also noted in Tm_D. Corcoran and Page suggest that myxedema exercises an effect on renal function, in part at least as a result of the reduction in the number of the eosinophilic cells of the adenohypophysis.[103–105]

The Gastrointestinal Tract.—As mentioned elsewhere in this chapter achlorhydria occurs in approximately half the patients.[97] Anorexia is common and may reflect the decreased food requirements. Constipation is the rule, probably related to the decrease in peristalsis. Absorption is greatly delayed, in part due to retarded gastrointestinal motility and in part to the decreased function of the mucosal cells. Tympanites and meteorism are common complaints.[137]

The Musculo-Skeletal System.—Muscle pains are not uncommon in myxedema and their occurrence is understandable in view of the extracellular infiltration of the skeletal muscles with edema and mucoid material. The muscle cell itself shows degeneration of the central portion of the sarcoplasm and the presence of vacuoles containing basophilic material.[45] These pathologic changes are similar to those encountered in cardiac muscle and in the involuntary musculature of the viscera. No specific alterations are observed in the joints, although some limitation of motion and joint pains are occasionally noted.

Retardation in bone growth and delay in epiphysial fusion are characteristic of the young hypothyroid. It is of considerable interest, however, that sexually mature women with myxedema may show incomplete closure of the epiphyses.[108] *This would suggest that estrogens alone may be insufficient to insure epiphysial closure.*

Nervous System Manifestations in Myxedema.—Vertigo and paresthesias of the extremities are common complaints. The origin of these symptoms is not clear, although anemia, which is so commonly present in myxedema, may play some role. Deafness occurs in one third of the cases and may be either of the conduction or nerve type. Marked improvement in the hearing of these patients is frequent after the administration of thyroid extract. Marked torpor, sluggishness, mental retardation and impaired memory are characteristic of this disease. The electroencephalogram generally shows an absence of the alpha waves and a decrease in the amplitude of the other brain waves.[106,154] Himwich and his associates[162] have shown that in cretins there is an increase in cerebral oxygen consumption of approxi-

mately 32 per cent following the administration of thyroid extract. This is reflected by electroencephalographic changes and acceleration of psychologic activity. Various organic psychoses are sometimes observed in myxedema, which can be cured with thyroid extract.[107,169] On the other hand, vigorous treatment with thyroid extract to the point of the production of hyperthyroidism in patients with myxedema may provoke acute psychotic episodes.

The Effect of Myxedema on Diabetes Mellitus.—Diabetes mellitus is markedly improved following the development of myxedema[1,9] and exacerbated with the administration of thyroid extract.[113,157,158,159] This effect of myxedema is not due to any primary role of the thyroid on carbohydrate metabolism but rather is related to a delay in the absorption of carbohydrates from the intestinal tract and the reduction in nutritional requirements. In myxedema *per se* the fasting blood sugar level may be normal or slightly reduced and the oral glucose tolerance curve is not infrequently flat. The intravenous glucose tolerance curve, however, is usually normal. When the patient with diabetes mellitus develops myxedema, because of the delayed glucose absorption and the decrease in food requirement there occurs a reduction in the blood sugar level and an amelioration of the clinical picture of the diabetes. The insulin requirement is usually markedly reduced. With the administration of thyroid extract and improvement in the clinical manifestations of myxedema, the blood sugar level rises, the symptoms of diabetes become more pronounced, and the insulin requirement proportionately increased.

Secondary Myxedema (Pituitary Myxedema).—This form of hypothyroidism and myxedema occurs in association with destructive lesions of the adenohypophysis. This problem has been discussed elsewhere in this book, but some points merit recapitulation. The diagnosis of pituitary myxedema should be suspected in the presence of functional failure of the other endocrine glands. Thus, the association of gonadal, adrenal and thyroidal insufficiency points to the pituitary origin of the endocrine dysfunction. Secondary myxedema is almost always associated with either clinically demonstrable evidence of adenohypophyseal destruction, as by tumor, or a history of a postpartum hemorrhage such as occurs in Sheehan's syndrome.[114–116,174] The presence of papilledema, ballooning of the sella turcica, or encroachment on the visual fields points to the presence of a primary pituitary destructive lesion.

In both primary and secondary myxedema there occurs a decrease in the urinary excretion of the neutral 17-ketosteroids and of the 11-oxygenated compounds. The reduction in the excretion of these steroids is more marked in the patients with secondary myxedema. Both groups show increased sensitivity to insulin as determined by the hypoglycemic responsiveness test, although here too the response of the patient with pituitary myxedema is more pronounced. The urinary excretion of gonadotropins is either markedly reduced or entirely absent in patients with secondary myxedema. In primary myxedema the value for the urinary gonadotropins is either normal or slightly reduced. Amenorrhea, which is almost uniformly present in women with pituitary myxedema, is less common than menorrhagia in primary myxedema.

The therapeutic response to thyroid extract is somewhat more satisfactory in patients with primary myxedema, although the group with pituitary myxedema will also show an increase in the basal metabolic rate and an improvement in the hypothyroid manifestations. Recently Peters and his coworkers[1-5] *described a group of patients with tumors of or near the* hypophysis associated with various degrees of adrenal, thyroid, and gonadal insufficiency. Most members of this group had considerable reductions in the basal metabolic rate and the serum protein bound iodine was within the range encountered in myxedema. However, these patients exhibited none of the clinical manifestations associated with hypothyroidism and the administration of thyroid extract resulted in neither an appreciable clinical change nor an increase in the serum precipitable iodine. Thyroid extract must be employed with caution in patients with pituitary myxedema since adrenal insufficiency may sometimes be precipitated.[1-6] With the availability of purified thyrotropin this agent may be used in the treatment of pituitary myxedema. However, patients with primary myxedema will not respond to this fraction.[194]

TABLE 28.—SIGNS AND SYMPTOMS IN 77 PATIENTS WITH MYXEDEMA (FROM LERMAN)

Symptom and Sign	*Percentage Incidence*	*Symptom and Sign*	*Percentage Incidence*
Weakness	99	Peripheral Edema	55
Dry Skin	97	*Hoarseness or Aphonia*	52
Coarse Skin	97	Anorexia	45
Lethargy	91	Nervousness	35
Slow Speech	91	*Menorrhagia*	32
Edema of Eyelids	90	Palpitation	31
Sensation of Cold	89	Deafness	30
Decreased Sweating	89	Poor Heart Sound	30
Cold Skin	83	Precordial Pain	25
Thick Tongue	82	Poor Vision	24
Edema of Face	79	Fundus Oculi Changes	20
Coarseness of Hair	76	Dysmenorrhea	18
Cardiac Enlargement (X-ray)	68	Loss of Weight	13
Pallor of Skin	67	Atrophic Tongue	12
Memory Impairment	66	*Emotional Instability*	11
Constipation	61	Choking Sensation	9
Gain in Weight	59	Fineness of Hair	9
Loss of Hair	57	*Cyanosis*	7
Pallor	5[illegible]	Dysphagia	3
Dyspnea	55		

Summary of the Signs and Symptoms in Myxedema.—The incidence of the various signs and symptoms in myxedema was carefully studied by Lerman.[49] These results are tabulated in the following table. By and large, the frequency incidence of symptoms recorded in these 77 cases is similar to that noted in the group of 45 patients from the same hospital

collected previously by Krantz.[179] Burnstein[65] collected 151 cases of adult hypothyroidism and myxedema. Of these 43 were instances of frank myxedema. The incidence of the individual symptoms was much less in his group, but it is possible that the punch card system used by Lerman would elicit and record symptoms that might pass unnoted on the routine chart. In Burnstein's series, the most frequent symptoms were fatigue (44 per cent), constipation (40 per cent), headache (35 per cent), backache (30 per cent), abdominal pain (26 per cent), general aches and pains (23 per cent), and nausea (21 per cent). The incidence of all the other symptoms was under 20 per cent. Other analyses have been made by Sturgis,[160] Rose,[179] Reilly,[189] and Pullen.[190] The nonspecific character of many of the presenting symptoms in hypothyroidism is obvious.

The Laboratory Findings in Myxedema.—In myxedema, the basal metabolic rate is markedly reduced, being usually in the range −30 to −45 per cent. In our own group of patients and in other series, the basal metabolic rate has been as high as −15 per cent. The basal metabolic rate may reach a low level some time before the more overt clinical manifestations of myxedema are evident. If thyroid medication is abruptly discontinued in an individual with athyreosis, the curve of the basal metabolic rate falls relatively rapidly to −30 per cent in twenty to thirty days and then more slowly approaches −40 per cent. Myxedema will return in approximately eighty days after the cessation of therapy.

With the fall in the basal metabolic rate, nitrogen excretion is decreased and large stores of protein are deposited as mucoproteins in the intercellular space.[144] The serum electrophoretic pattern shows a low plasma albumin, a reduction in the alpha globulin, and an increase in the beta globulin fractions.[161] This last finding is associated almost invariably with hypercholesterolemia.[165] The spinal fluid protein is increased in most instances. This, as well as the mild albuminuria so often encountered, probably reflects an increase in capillary permeability. The blood cholesterol is frequently increased in hypothyroidism[119, 1 3, 133] but may often be within the normal range.[117, 118, 1 0] One of the earliest signs of response to thyroid therapy is a reduction in the serum cholesterol regardless of the original serum level.[117] The serum phospholipids are usually elevated when the cholesterol is increased, but the concentration of neutral fats in the serum is unaltered. This is in contrast to what is observed in pituitary myxedema, where the serum concentration of neutral fats is very frequently increased.[1 5] This observation in secondary myxedema may be related to the associated impairment in adrenal cortical function. Carotenemia may be noted in myxedema, since *the blood carotene level is frequently elevated*.[136] The vitamin A content of the blood, however, may be reduced.

The serum bound magnesium or non-diffusible fraction is low or absent. This value returns to normal levels following the administration of thyroid extract. The total serum magnesium, however, is within the normal range.[137] The serum alkaline phosphatase is generally decreased in hypothyroidism and myxedema and increased with therapy with thyroid extract.[161] The urinary excretion of creatine and the creatine tolerance test is similar in individuals with myxedema to that observed in normal subjects. In both groups the spontaneous daily urinary excretion is less than 50 mgm

However, the administration of small doses of thyroid extract will result in a marked creatinuria and in impairment of the creatine tolerance test in patients with myxedema, while normal individuals will remain relatively unaffected by similar therapy.[126, 127]

The urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated steroids is reduced in myxedema but return to normal levels with thyroid extract therapy.[1, 9, 130]

The serum protein-bound iodine is almost invariably less than 4 micrograms (gamma) per cent in myxedema.[138–141] With the administration of thyroid extract, the serum protein-bound iodine rises at a rate of 2 gamma per cent per grain of extract.[138, 14] The elevation in serum protein-bound iodine usually precedes the increase in the basal metabolic rate. As described in a previous chapter, the collection of radioactive iodine by the thyroid gland or the urinary excretion of this isotope following the administration of a tracer dose may be employed as a measure of thyroidal activity.[145–153] In general, in patients with hypothyroidism or myxedema the urinary excretion of radioactive iodine is greater and the thyroid collection less than in the euthyroid individual. However, the overlapping of the values encountered in these two groups is so great as to render this an inadequate method for the diagnosis of myxedema in contrast to the value of this test in hyperthyroidism. The twenty-four hour urinary excretion of radioactive iodine may vary in patients with myxedema, according to Oshry and Schmidt,[154] from 48 to 93 per cent, in contrast to 42 to 80 per cent in euthyroid individuals. The collection of the radioactive isotope by the thyroid is more satisfactory as a measure of underfunction of the thyroid gland, according to Werner and his coworkers.[149, 150] These investigators found that in normal individuals the uptake of radioactive iodine varies from 10 to 35 per cent in twenty-four hours, whereas in patients with myxedema the thyroid collection varies from 1 to 4 per cent.

The Differential Diagnosis of Myxedema.—Myxedema must be differentiated particularly from *non-thyrogenous hypometabolism*, from *chronic diffuse glomerulonephritis* in the *nephrotic stage*, from *pernicious anemia* and finally from some *primary psychoses* and *cerebral arteriosclerosis*. Non-thyrogenous hypometabolism is characterized by the presence of a low basal metabolic rate without any of the clinical manifestations of myxedema. The serum protein-bound iodine is normal in such individuals. There is a minimal or no therapeutic response to the administration of thyroid extract.

Chronic diffuse glomerulonephritis in the nephrotic phase is characterized by edema, pallor, swelling of the face and enlargement of the heart which may superficially resemble myxedema. The basal metabolic rate is often markedly lowered and the serum cholesterol level elevated. Indeed, thyroid extract was previously advocated for the treatment of the nephrotic syndrome.[123] However, the presence of a marked albuminuria and other evidence of renal damage, as well as the pronounced reduction in the serum protein with a reversal of the albumin globulin ratio will direct attention to the renal origin of the syndrome. Patients with myxedema may show a mild albuminuria and perhaps some decrease in the serum protein level, but neither of these findings is present to the extent

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Patients with pituitary myxedema must be treated cautiously with thyroid extract or thyrotropin. In such individuals impairment of adrenal cortical function may be present and the injudicious use of the thyroid hormone may induce acute adrenal cortical insufficiency.[116]

Patients with myxedema heart, particularly when other etiologic forms of heart disease are present, must be treated with great care. In such individuals there is the risk of overburdening the heart and circulation as a result of the increase in the basal metabolic rate. Congestive heart failure and anginal episodes may thus be precipitated. Treatment in this group is begun with 10 mgm (1/6 grain) of thyroid extract daily and slowly and cautiously increased. It is important to remember that patients with myxedema tolerate morphine and other sedatives poorly and minute doses may induce deep lethargy.[193]

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observed in nephrosis. Finally, the serum neutral fat is generally considerably increased in nephrosis but remains unaltered in primary myxedema.[117] The serum protein bound iodine may be reduced in the nephrotic syndrome but no change occurs following treatment with thyroid extract.[117]

The Treatment of Myxedema. — The agents generally available for the treatment of myxedema are: 1, desiccated thyroid extract; 2, thyroglobulin; and 3, thyroxine. The introduction of thyrotropin makes available another agent for the treatment of pituitary myxedema. Both desiccated thyroid extract and thyroglobulin are efficacious when given orally. Thyroxine, however, is comparatively insoluble, poorly and irregularly absorbed from the gastrointestinal tract, and is therefore administered intravenously. Thyroxine has no great advantages over desiccated thyroid extract. Iodocasein is also efficacious in athyreosis and its relative potency has recently been studied.[160, 175, 176, 177] Boothby and his coworkers[191] have shown that in a totally athyreotic individual the effect of a single intravenous injection of thyroxine may persist for as long as seventy to eighty days, although in most instances its effect is dissipated within three to four weeks. Following the intravenous injection of thyroxine there is an increase in the basal metabolic rate which reaches a peak within seven to ten days and then begins to decline. There is a difference in sensitivity between normal individuals and patients with myxedema to both thyroid extract and thyroxine. Individuals with euthyroidism will tolerate 1½ to 3 grains of thyroid extract daily without sustaining any increase in the basal metabolic rate.[127, 128] According to Means,[49] however, a daily oral intake of 30 milligrams (½ grain) of thyroid extract U.S.P. will keep the basal metabolic rate of a myxedematous patient at a level of approximately −20 per cent. From 1 to 3 grains daily is required to maintain the basal metabolic rate at a level of −10 to 0.0 per cent. One milligram of thyroxine administered intravenously daily will increase the basal metabolic rate of a myxedematous subject by 2.5 per cent a day. By the same token, since myxedematous patients are more sensitive to the thyroid hormone than are normal individuals, signs of thyroid intoxication may be more readily induced in the former. In general, the activity of desiccated thyroid extract is proportional to its total organic iodine content. The organic iodine content of standard U.S.P. XIII preparations of desiccated thyroid extract may vary from 0.17 to 0.23 per cent. Each milligram of thyroxine contains 0.65 mgm. of iodine.

The results obtained in patients with myxedema treated with thyroid extract are most satisfactory. Such individuals may be restored to a normal state in almost all respects. Treatment is usually begun with small doses of thyroid extract varying from 15 to 30 mgm. daily and increased gradually until the subjective and objective evidences of myxedema disappear. In general, the total daily requirement is administered in one dose, usually before breakfast, although it may be given at any time of the day. Treatment must be continued throughout the life of the individual and cessation of therapy will be followed by a return of the myxedematous state within a period of one to three months. A successful attempt at the transplantation of thyroid tissue in myxedema was described by Loup.[163]

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It is convenient for purposes of discussion to refer to all of these syndromes as manifestations of Graves' disease. In the discussion that follows however the special considerations involved in each type of syndrome will be more fully developed.

Etiology.—The etiology of Graves' disease is unknown. It has been repeatedly noted however that psychic trauma may precede the onset of the disease.[7-10] Conrad[10] has claimed that she has been able to elicit a history of emotional upset in 94 per cent of patients with hyperthyroidism. However most observers although not employing detailed psychiatric technics have been unable to obtain as high an incidence of preceding emotional stress. It is of interest that the incidence of Graves' disease was extremely low in the armed forces in spite of the fact that careful search was made for evidences of this disorder. Nevertheless at home the onset of thyrotoxicosis was often preceded by the receipt of unfavorable news concerning relatives. The army personnel of course represents a highly selected population carefully screened by physical and psychiatric tests. It is equally possible that the circumstances and type of stress encountered in military life may not be conducive to the production of this illness.

Since the administration of thyrotropin will stimulate the thyroid to hyperplasia and hyperfunction and induce exophthalmos in the experimental animal it is believed that the primary mechanism involved in the production of hyperthyroidism is a release of excessive amounts of this fraction from the adenohypophysis. This is in part substantiated by the fact that the administration of large quantities of thyroid hormone may result in hyperthyroidism but does not produce exophthalmos.

The question arises concerning the status of the adrenal cortex in thyrotoxicosis. There is evidence which would point to the presence of some impairment of adrenal cortical function in this disease. Clinically patients with Graves' disease may manifest asthenia and pigmentation resembling that observed in Addison's disease. In addition the presence of a diffuse lymphadenopathy, lymphocytosis and often an increase in circulating eosinophils as well as a decrease in the urinary excretion of the neutral 17-ketosteroids and the 11-oxygenated compounds suggests impairment of adrenal cortical function. LeCompte[4] has described a reduction in the width of the adrenal cortex in Graves' disease. The interrelationship between the thyroid and adrenal cortical function was further emphasized by the work of our group.[44] We found that the uptake of radioactive iodine by the thyroid of the experimental animal could be influenced by variations in the level of adrenal cortical activity. In the bilaterally adrenalectomized animal the administration of epinephrine caused an increase in the uptake of radioactive iodine by the thyroid. This increase in function could be inhibited by the administration of 17-hydroxy-11-dehydrocorticosterone (Cortisone).[44] In further studies we demonstrated that the uptake of I_{131} could be inhibited by the exogenous administration of ACTH in both the intact and adrenalectomized animal. If a similar mechanism is operative in the human then the pathogenesis of hyperthyroidism could conceivably be as follows. When an individual is subjected to alarm or stress the discharge of epinephrine from the medulla will result in an

Chapter 26

HYPERTHYROIDISM (GRAVES DISEASE) DIFFUSE AND NODULAR TOXIC GOITER MALIGNANT EXOPHTHALMOS

Parry[1] and later Graves described a clinical syndrome characterized by exophthalmos diffuse goiter and symptoms which we now know to be due to hyperthyroidism On the Continent Basedow[3] independently described this same disorder It has become apparent that the hypermetabolic symptoms resulting from overproduction of the thyroid hormone may or may not be associated with the eye signs so characteristic of Graves disease Indeed it has often been noted that thyrotoxicosis found in conjunction with a nodular goiter is usually not characterized by the presence of exophthalmos whereas protrusion of the eyes is a very frequent manifestation of diffuse toxic goiter Furthermore the eye signs noted in Graves disease may be found in conjunction with the euthyroid or even the hypothyroid state

As a result of the various combinations of symptoms and signs that may be encountered clinically separate and distinct names have been given to the various forms of the disease Explanation of these terms is therefore necessary *Hyperthyroidism* and *thyrotoxicosis* are synonomous and refer to the metabolic manifestations due to excessive production of thyroid hormone The term *toxic goiter* refers to thyrotoxicosis associated with enlargement of the thyroid gland of a diffuse or nodular character *Graves disease* in the sense originally described is a syndrome characterized by thyrotoxicosis ophthalmopathy and diffuse thyroid enlargement Common usage however has applied the term to all forms of thyrotoxicosis with or without eye signs and even to the pure ophthalmic syndrome *Toxic nodular goiter* refers to thyrotoxicosis associated with a nodular goiter Plummer[6] advanced the hypothesis that this type of goiter presented a different clinical picture than did diffuse toxic enlargement and that the manifestations of toxicity were due entirely to overactivity in the nodule Most observers in the past however have felt that the hyperthyroidism was a manifestation of overactivity of the entire gland the nodule representing a residuum of previous irregular hyperplasia and involution Recent studies with radioactive iodine have revealed that some instances of toxic nodular goiter are actually due to overactivity of the nodule itself In most instances however the hyperthyroidism is the result of increased activity of the entire gland the nodular areas being relatively inactive[6,171,172] The syndrome associated solely with eye signs has been variously referred to as *hyperophthalmic Graves disease*[4] *exophthalmic ophthalmoplegia* and *malignant exophthalmos*[21]

dark staining The acini are larger and the solid islands of epithelium *which are noted in the untreated gland are less abundant*

In the thyroid of the patient with toxic nodular goiter the hyperplasia and hypertrophy may be diffuse or localized to the nodule or even to the *extranodular tissue Following iodine therapy involutionary changes are* observed wherever hyperplasia had previously been present Enlargement of the thymus lymph nodes and spleen are frequently observed[3] This *is part of the hyperplasia of lymphatic tissue so commonly encountered in* hyperthyroidism The pituitary gland may be enlarged and the percentage of chromophobe cells in the adenohypophysis is often increased while the *percentage of eosinophils is decreased* The *basophil cells according* to Kraus[22] frequently show vacuolization Means[11] however found no abnormalities in the hypophysis in 4 patients and Holst[19] was unable to

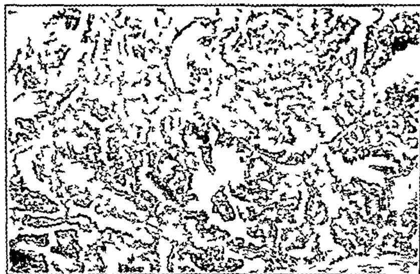


FIG 82 —Exophthalmic goiter Note thyroid hyperplasia with decrease in colloid (Courtesy Dr W D Collier)

find any significant changes in the group he studied No constant changes have been noted in the parathyroid glands Rarely the gonads may show some atrophic changes[13] The findings in the adrenal cortex are of interest Although in the experimental animal exogenous thyroid intoxication results in adrenal cortical hypertrophy in the thyrotoxic patient the adrenal cortex is narrowed[4] At postmortem examination the heart is enlarged and hypertrophied in approximately half the cases[3,6,27] However studies by Friedberg and Sohval[23] would indicate that the cardiac hypertrophy observed in hyperthyroidism is generally associated with other etiologic factors except in those instances in which auricular fibrillation is present The histologic findings in the heart are inconstant and not particularly characteristic of hyperthyroidism *It is possible that the lymphocytic and* histiocytic infiltration as well as the myocardial necrosis and fibrosis so

increase in the elaboration of both adrenocorticotropin and thyrotropin from the adenohypophysis In normal individuals the adrenocorticotropin will then stimulate the adrenal cortex with the secretion of adrenal cortical fractions which will in turn inhibit the further elaboration of thyrotropin as well as adrenocorticotropin In addition, the adrenocorticotropin thus elaborated may directly inhibit the hypophyseal secretion of thyrotropin In potentially hyperthyroid persons, however there may be either an inadequate secretion of adrenocorticotropin or a primary defect in adrenal cortical response In both instances there would occur an inadequate elaboration of those hypophyseal or adrenal cortical fractions necessary to insure inhibition of thyrotropin secretion

Graves disease may occur at any age The greatest frequency, however, is noted between the ages of twenty and forty years The incidence of the disorder is far greater in females than in males In regions where goiter is non endemic the female preponderance is in a ratio of 4 to 1 [11] In endemic areas this ratio is much lower being 4 to 3 [13] an incidence similar to that of nontoxic goiter in the same region [12] suggesting a relationship between toxic and nontoxic goiter [12] It was claimed by McClendon and Hathaway [14] that the geographic distribution in the United States of simple goiter and hyperthyroidism was similar However in Sweden no such correlation was noted [15] Finally it is evident that there is no dearth of thyrotoxicosis in non-endemic areas A familial incidence of the disorder has been noted by various observers [17,106]

Of great interest is the recent report of Iversen[18] on an epidemic wave of thyrotoxicosis in Denmark during World War II Although Plummer[19] had previously reported an epidemic rise in the incidence of thyrotoxicosis in Olmsted County, Minnesota in the years 1924 to 1927 it is possible that this represented simply an increase in frequency of hospitalization of the afflicted individuals The Danish epidemic was apparently unrelated to the stress of German occupation since no such increase occurred in occupied Belgium Holland or Norway It was probably unrelated to diet and in due time the epidemic spontaneously subsided A suitable etiologic explanation for the epidemic is still lacking

The Pathology of Graves Disease —In diffuse goiter associated with Graves disease the thyroid is firm enlarged and hyperplastic Grossly it may be red in color as a result of the marked vascularity [20] The cut surface of the gland appears meaty and no colloid is visible The microscopic examination reveals the cells to be tall columnar Cytologic evidences of the hyperplasia include hypertrophy of the Golgi apparatus [0] and an increased number of mitochondria [1]

The follicles contain scant amounts of a pale staining colloid The follicular epithelium is elevated and folded in papillary like projections that encroach on the lumen of the acini Distributed throughout the highly vascular interstitium there are large and small lymphoid follicles If the gland is removed following the administration of iodine to the patient marked involutionary changes occur The height of the follicular epithelium is reduced the cells appear cuboidal and colloid is abundant and

and the eye signs and the nervous and emotional symptoms are marked. Tachycardia is common, but auricular fibrillation is infrequent. In toxic nodular goiter, on the other hand, there is usually a history of goiter antedating the onset of the symptoms. The patients are usually past the age of forty. The eye signs and emotional manifestations are minimal, but auricular fibrillation and heart disease are common. The frequency with which recurrence occurs following surgery is much less in the latter group than in the former.

However, inasmuch as many of the manifestations in both diffuse and toxic nodular goiter are similar, we shall discuss the manifestations of both types of syndrome together, pointing out where necessary the details in which they differ.

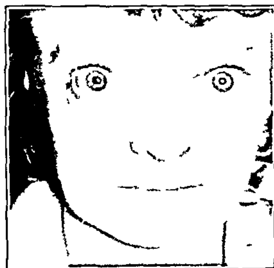


Fig 83 —Recurrent Graves' disease with severe exophthalmos

Although the thyrotoxic patient may be of any age, the group most frequently affected is between twenty and forty years of age. The disease is much more common in females, being 4 times as frequent as in males. There is no characteristic bodily habitus. We have observed both obese and emaciated patients with thyrotoxicosis. For the most part, their nutritional status appears to be adequate, probably because the ravenous appetite so often present in this disorder has prevented more than a moderate weight loss. The typical facies is characterized by prominent or bulging eyes and an anxious, unblinking expression. The hands tremble, the skin is warm and moist, and the patients tend to speak volubly and rapidly. They fidget constantly and are rarely at rest. This clinical picture is that of a patient with diffuse toxic goiter.

In toxic nodular goiter the clinical manifestations may be similar, except for the absence of the striking eye signs. In this group the eyes may be bright and glittering but exophthalmos is uncommon. The so-called

often observed represent the result of ancillary pathologic processes such as coronary sclerosis rather than hyperthyroidism.[9–21]

In approximately 90 per cent of the patients with thyrotoxicosis the liver may show marked fatty changes with focal and sometimes central areas of necrosis.[3–35] These changes may be extensive enough to result in atrophy and occasionally in cirrhosis. The cirrhotic changes are characterized by dilatation of the portal canals with a periportal lymphocytic infiltration. A network of thin strands of connective tissue unite the affected canals and impart a fine nodularity to the liver. Beaver and Pemberton[35] have studied the liver at postmortem examination in 107 patients with thyrotoxicosis. They found that the hepatic lesions were predominantly of three types. The most common lesion was that of acute degenerative changes with fatty infiltration and focal and central necrosis. The next most common change observed was that of atrophy, which was present in two thirds of the patients. In these instances the average weight of the livers was 1,316 grams. Subacute toxic atrophy and cirrhosis, which was the third type of alteration encountered, was present in over half the cases. It is important to emphasize that these observations were made in patients who died of hyperthyroidism and therefore probably represent extreme changes. More recent studies in which liver puncture biopsies were performed for the most part failed to reveal these changes.[38]

Although lymphocytic infiltration of the skeletal musculature has been reported, these changes are by no means constant. Such lymphocytic infiltration may also be observed in the musculature of the eyeball.[39, 9] Recent studies conducted in our laboratory[40] have demonstrated that exophthalmos in the guinea pig induced by the administration of thyrotropin is associated with a marked increase in the mucoprotein and water content of the retro-orbital tissue. A similar substance is found in the pretibial myxedema sometimes encountered in association with postoperative severe exophthalmos.[41, 4, 8, 134–138]

The Signs and Symptoms of Graves' Disease. – The signs and symptoms observed in Graves' disease are mostly the result of the excessive production of thyrotropin by the adenohypophysis and of the thyroid hormone by the thyroid gland. Our present conception of the pathogenesis of diffuse toxic goiter envisages the excessive production of thyrotropin which stimulates the thyroid gland to hypertrophy and hyperplasia with the resultant elaboration of more thyroid hormone than is necessary for purely physiologic needs. In addition to this fundamental action of thyrotropin, there is some evidence to indicate that this fraction exercises a direct effect on some tissues other than that of the thyroid gland. Malignant exophthalmos and pretibial myxedema probably represent such effects, while the other clinical manifestations of Graves' disease are due to the presence of excessive amounts of thyroid hormone. The clinical symptomatology associated with toxic adenoma, in contrast to that observed in diffuse toxic goiter, would suggest that all of the manifestations in the former group were due to the thyroid hormone alone.

In comparing the clinical manifestations of diffuse toxic goiter and toxic adenoma, the symptoms and the goiter appear concomitantly in the former usually prior to the age of thirty-five. The thyroid is diffusely enlarged

The Circulation in Hyperthyroidism —The augmented metabolic requirements of the patient with thyrotoxicosis increase the burden on the circulation In an effort to compensate for the increment in the metabolic needs of the tissues both the cardiac output and the circulatory rate are markedly increased The increase in the cardiac output is effected chiefly by an acceleration in the heart rate and minimally if at all by an increase in stroke volume [49 51] It is for this reason that patients with hyperthyroidism have a marked tachycardia which is present while the patient is awake and asleep [40] Since the oxygen requirement of the body may be increased as much as 50 to 100 per cent the cardiac output may be doubled It may however be augmented even more than the increase in oxygen requirement would suggest for the arteriovenous difference is almost always reduced in thyrotoxicosis [41] The circulation time is markedly accelerated and in the absence of heart failure is generally less than ten seconds when measured from arm to tongue [52 53] Although Blumgart and his coworkers[53] have reported a direct correlation between the circulatory rate and the basal metabolic rate this is not consistently observed The circulating blood volume is increased by approximately 10 per cent [54] In Graves disease the blood flow through the skin is increased In normal subjects only 3 per cent of the cardiac output is routed through the skin while in hyperthyroidism 6 per cent of the output flows through the cutaneous vessels [55] Direct observation of these vessels by means of capillary microscopy reveals the marked dilatation [56] which is probably at least in part the result of increased tissue metabolism The venous return is increased and contributes to the augmented cardiac output The work of the heart is performed much less efficiently in a patient with thyrotoxicosis than in the normal subject [36 57] Exercise or any factors which increase the cardiac load are carried out only at the cost of excessive increases in cardiac output and oxygen consumption It is for this reason that heart failure is more likely to occur in the thyrotoxic patient when hypertension or coronary artery disease further lessen the efficiency of the heart

The subjective symptoms of which the patients with hyperthyroidism frequently complain are palpitation exertional dyspnea and precordial pain Palpitation may accompany the tachycardia or may represent premature contractions or paroxysmal episodes of auricular fibrillation or rarely auricular flutter It is possible that the sensation experienced may reflect the hyperactivity of the venticular muscle A throbbing sensation in the neck due to the marked pulsation of the neck vessels is a frequent complaint Since the ordinary oxygen needs of the resting thyrotoxic patient are increased and the vital capacity is decreased [58] minimal or moderate exertion will be reflected in dyspnea which is not necessarily the result of heart failure This is particularly true in places of high altitude where dyspnea is one of the most common complaints noted in thyrotoxicosis The precordial pain which is sometimes encountered is usually mild and of a dull and aching character This symptom was complained of in 16 per cent of the group of patients reported by Lerman and Means [38] At times true angina pectoris may occur This may be due to episodes of paroxysmal arrhythmia or it may be the result of the increased strain of

apathetic Graves' disease in which the symptoms of hyperthyroidism are subdued, is much more frequently encountered in toxic nodular goiter than in toxic diffuse goiter

In thyrotoxicosis the hair and skin are thin and of a smooth silky texture.[46] The skin is warm and moist and sweating is increased. These patients usually manifest intolerance to heat and prefer cold to hot weather. An erythema is commonly noted over the pressure areas particularly over the elbows, knuckles and thenar and hypothenar eminences of the palms. Dermatographia can generally be readily elicited. Although in 50 per cent of the patients increased pigmentation of the skin is noted, the mucous membranes remain free.[46] Vitiligo occurs in approximately 10 per cent. Alopecia of the scalp may occur during the course of the illness and Williams[5] has pointed out that the axillary hair is markedly decreased. Premature graying of the hair may be encountered. The nails may exhibit longitudinal or transverse grooves. In the male gynecomastia is occasionally seen. This may be due to the associated liver damage with impaired estrogen detoxification.

Goiter is usually present although instances of functional thyroid hyperactivity without anatomic enlargement do occur. It should be emphasized that the gland may be intrathoracic and hence may not present at its usual location. In such instances it could be detected only by roentgen examination. In diffuse enlargement of the thyroid the gland remains smooth and becomes firm to the touch. The increase in size is usually symmetrical but one lobe may be larger than the other. In toxic nodular goiter the gland is irregularly enlarged. In toxic goiter the gland becomes markedly vascular and a thrill may be palpable or a bruit audible. Such findings are of great confirmatory value in establishing the diagnosis. However they are not always present nor necessarily pathognomonic since a bruit is occasionally heard over a nontoxic goiter. A thrill however is rarely felt in the absence of thyrotoxicosis.[13] Lerman[13] found a bruit to be present in 77 per cent and a thrill in 38 per cent of patients with thyrotoxicosis.

Pressure symptoms may result from enlargement of the thyroid although this occurs more commonly in association with the nodular variety. Such symptoms however are much less frequent in toxic than in nontoxic goiter. Evidences of pressure are cough, some difficulty in breathing and swallowing, and compression of the trachea and occasionally of the esophagus. Hoarseness is unusual although a recurrent nerve type of paralysis of the vocal cord occasionally occurs. This manifestation is far more common in malignancy and inflammatory disease of the thyroid than in thyrotoxicosis.

The presence of a goiter is so frequent in hyperthyroidism that if none is readily apparent, one should search for an aberrant location of the gland. Not only may the gland reside anywhere along its embryologic course from the base of the tongue to its adult location in front of the trachea, but it may be found in a retrosternal or intrathoracic position. The x ray is of great importance in demonstrating the existence of the gland in these regions. Further help may be obtained by the use of profile studies with radioactive iodine.[164]

and uncomplicated thyrotoxicosis.[60] The incidence of congestive failure markedly increases after the onset of auricular fibrillation. One half of this latter group manifests congestive failure, an incidence which is four times as great as that observed in patients with normal rhythm.[59] Similarly, half the patients with heart failure and thyrotoxicosis have auricular fibrillation.[60] Lahey and Hurxthal[63] found that with the correction of the hyperthyroid state cardiac compensation could be permanently restored in 95 per cent of their patients. The usual therapeutic measures employed for heart failure are relatively ineffective until the thyrotoxicosis is controlled. It is perhaps important to emphasize that the clinical picture of hyperthyroidism may be overshadowed by intractable congestive failure. Such masked hyperthyroidism should be suspected where heart failure or irregularities of cardiac rhythm which are usually amenable to proper therapy fail to respond. Yohalem, Bartin and Silver[219] studied the urinary excretion of radioactive iodine and the serum protein bound iodine in 55 patients with continuous auricular fibrillation in whom overt clinical evidence of thyrotoxicosis was lacking. In 8 patients of this group the twenty-four hour urinary excretion of I_{131} was less than 20 per cent, and in another 5 patients was between 20 and 50 per cent. In 8 of these 13 patients the serum protein bound iodine was above 8 micrograms per cent. It would seem, then, that 15 per cent of this group of 55 patients with auricular fibrillation had masked hyperthyroidism.

Hepatic Manifestations.—Jaundice is rarely encountered in hyperthyroidism. Since this complication appears in the severe thyrotoxic state and commonly as a terminal phenomenon, its rarity today may be due to the early institution of treatment. At the Lahey Clinic jaundice was encountered in 0.5 per cent of patients with hyperthyroidism,[61] while in our hospital it occurred in 2 of 26 fatal cases of thyrotoxicosis.[58] However, evidence of impaired hepatic function may be demonstrated in 90 per cent of patients with Graves' disease when a battery of liver function tests are employed.[59] Thiamine deficiency, so often present in hyperthyroidism, may contribute to the functional impairment of the liver.

Gastrointestinal Symptoms.—The appetite is usually ravenously increased, although anorexia has been noted in some patients. Despite the increase in appetite and food intake, weight loss is almost always present. Nausea and vomiting are uncommon, but looseness of the bowels and even diarrhea is frequent. Achlorhydria is present in one third of the patients, but free hydrochloric acid may return with the successful treatment of the hyperthyroidism.[66,67]

The Blood in Hyperthyroidism.—The red blood cell count and hemoglobin are usually at normal levels. The total white blood cell count is often somewhat reduced and the differential study reveals a relative lymphocytosis.[64] An absolute increase in the monocytes has been reported.[65] A reduction in the neutrophilic leukocytes usually occurs, but the eosinophils may be increased to 3 to 6 per cent. Lymphadenopathy is frequent in hyperthyroidism, and although the spleen is usually enlarged it is not often palpable.

Genitourinary Manifestations.—The menses are generally not particularly disturbed in hyperthyroidism, but oligomenorrhea or even amenor-

the thyrotoxicosis on a heart with coronary arteriosclerosis Both types of angina may be alleviated by the treatment of the thyrotoxicosis

On examination the cardiac apical impulse is easily detected because of its forcefulness Clinically in uncomplicated thyrotoxicosis the heart is usually not enlarged but the sounds are loud and thumping in character The first apical sound is often accentuated and may be confused with that heard in mitral stenosis Both basal sounds are increased in intensity and a systolic murmur may be audible over the whole precordium In addition there is dilatation of the pulmonary artery which can be demonstrated by a teleroentgenogram of the heart The systolic blood pressure is usually increased and the diastolic pressure is slightly decreased with a resultant high pulse pressure The carotid vessels pulsate forcibly and reflect this increase in the pulse pressure

Paroxysmal auricular fibrillation was encountered in 10 per cent of a series of 7000 patients with hyperthyroidism and continuous auricular fibrillation occurred in 6 per cent [59, 60] The latter is generally, although not always preceded by paroxysmal episodes Auricular fibrillation occurs much more commonly in toxic nodular goiter than in diffuse goiter It is relatively uncommon before the age of forty five years and is rare under the age of thirty it occurs with a somewhat greater frequency in males Episodes of paroxysmal auricular fibrillation particularly in the younger age groups should raise the suspicion of the presence of hyperthyroidism In the older age group the incidence of auricular fibrillation increases in proportion to the duration of the thyrotoxicosis [59, 60] Neither paroxysmal nor continuous auricular fibrillation respond satisfactorily to treatment with either quinidine or digitalis unless the underlying hyperthyroidism is brought under control Following the successful treatment of the thyrotoxicosis the episodes of paroxysmal auricular fibrillation will generally eventually cease although such episodes occurring at infrequent intervals may continue for years One third of the patients with continuous auricular fibrillation will be spontaneously restored to normal rhythm following the successful treatment of the hyperthyroidism and in a considerable percentage of the remainder normal sinus rhythm will be established with the aid of quinidine

On fluoroscopic and roentgenologic examination the heart is usually found to be normal in size The pulsations of the left ventricle are forceful the pulmonary artery segment is prominent but no enlargement of any of the cardiac chambers is demonstrable The presence of cardiac enlargement usually suggests the coexistence of some other form of heart disease although it may occur in the presence of continuous auricular fibrillation or heart failure The electrocardiogram in hyperthyroidism is usually characterized by prominent P waves in all leads [6] The T waves may be high but this is an inconstant feature

The development of congestive heart failure is rare in uncomplicated thyrotoxicosis and particularly uncommon in patients under the age of forty When other forms of heart disease complicate hyperthyroidism heart failure has been reported to occur in 25 per cent of the patients [60] This is in contrast to an over all incidence of only 4 4 per cent in a series of 1000 patients which included various age groups and both complicated

Creatinuria is usually found Lymphocytic infiltrations of the muscles similar to that seen in myasthenia gravis have been reported [7] although prostigmine is of no value in treatment Complete recovery is to be expected after cure of the hyperthyroidism [5] When myasthenia gravis is present in association with thyrotoxicosis the former is aided by prostigmine but not by thyroidectomy [7, 49] Myotonia on the other hand has been reported in myxedema *Following treatment of the hypothyroidism* the signs of the myotonia disappear [9, 51] The most important muscular disorder encountered in hyperthyroidism however is that of exophthalmic ophthalmoplegia [7]

The Eye — The eye signs may be classified as 1 the lid signs 2 the *external changes in the lids or eyes* 3 the *extraocular palsies* and ptoses and 4 exophthalmos The lid signs may occur in either diffuse or nodular toxic goiter as well as in simple nontoxic adenoma and occasionally in individuals free from thyroid disease The external changes which are less common in occurrence than the lid signs are observed more frequently in diffuse toxic goiter but are also seen in toxic adenoma The rare extraocular palsies and ptoses are found almost exclusively in diffuse toxic goiter This is equally true of exophthalmos [3, 5, 6, 52–56]

The lid signs are several in number Widening of the palpebral fissure on fixation (Dalrymple s sign) is due to lid retraction It is noted in 9 per cent of patients with toxic adenoma and in 18 per cent of patients with diffuse goiter [52] Lid lag (Von Graefe s sign) is much more frequent occurring in 4 out of 5 patients with diffuse toxic goiter in 2 out of 3 with toxic nodular goiter and in 1 out of 3 patients with simple nontoxic goiter [52] Infrequent blinking (Stellwag) absence of gaze (Jeffroy) difficulty in eversion of the lid (Gifford) and tremor of the closed lid (Rosenbach) are other lid signs observed less frequently The exact mechanism for the production of these signs is unknown Among the possibilities suggested are those of central nervous system changes similar to those encountered in encephalitis and instability of the autonomic innervation of the eye In any event any explanation must account for the relaxation of the *orbicularis oculi the contraction of the levator palpebrae* and the tonic contraction of the involuntary smooth muscles of the lids

The external ocular changes include weakness of convergence (Moebius) pigmentation of the skin of the lids (Jellinek) dilatation of the pupil following the instillation of adrenalin into the conjunctival sac (Loewi) and excessive lacrimation The genesis of these signs is similarly obscure

The extraocular palsies are rare occurring in approximately one third of 1 per cent of patients with diffuse toxic goiter [70, 5] They may be divided into two groups The first group consists of single or multiple extraocular palsies associated with exophthalmos and severe thyrotoxicosis Complete bilateral or unilateral ophthalmoplegia with or without ptosis may occur Following correction of the hyperthyroidism the exophthalmos and palsies usually improve In this group there is a tendency for the muscles of elevation to be impaired first but any muscle may be involved and different muscles in each eye may become paretic

The other group of ocular palsies and exophthalmos occurs in association with *mild hyperthyroidism and even occasionally without hyperthyroid-*

rhea may be present Menorrhagia is less frequently observed Sterility is somewhat increased in both males and females with hyperthyroidism

Renal function is unimpaired and despite the increase in the urinary excretion of calcium, renal calculi are only rarely encountered [269]

The Skeletal System in Hyperthyroidism —Hyperthyroidism is frequently associated with decalcification and osteoporosis As a consequence of the bony alterations collapse of one or more vertebrae may rarely occur Thyroidectomy or the medical correction of the thyrotoxicosis will result in amelioration of the bone pain but usually there is little or no x ray evidence of recalcification The x ray picture encountered in hyperthyroidism is that of bone atrophy The cortex becomes thin, but there are no erosive processes or cysts or giant cell tumors and no dilated Haversian canals are seen The serum calcium phosphorus and alkaline phosphatase levels are normal [137] However anatomically cases have been reported in which in addition to evidences of osteoporosis extensive osteitis fibrosa is found [138] Albright and Reifenstein[45] believe that most of the skeletal manifestations may represent the secondary effects of nitrogen wastage and in those patients in the menopause are the effects of senile osteoporosis

Neuropsychiatric and Muscular Manifestations in Hyperthyroidism.—The thyrotoxic individual is markedly hyperkinetic It has been suggested by Waldenstrom[70] that the depletion of the body stores of iodine produces many of the neurologic phenomena of hyperthyroidism including paraphasia acalculia psychosis with hallucinations bulbar palsy coma, myoencephalopathy and choreoathetotic movements These occur especially he says in thyroid crisis and are markedly ameliorated by the administration of iodine

Psychoses may be precipitated by the onset of thyrotoxicosis It is particularly important that these patients be treated promptly since cure or amelioration of the psychotic state often follows the successful treatment of the thyrotoxicosis It seems likely that hyperthyroidism *per se* does not produce a psychosis but allows a dormant psychotic state to become manifest Indeed no special type of psychosis was noted in a large series of patients with hyperthyroidism studied by Dunlap and Moersch [71] The most commonly encountered types were toxic exhaustion occurring chiefly in the young patients with exophthalmic goiter acute delirium noted frequently in the older individuals with nodular toxic goiter and manic-depressive states

Muscle disorders are frequently associated with hyperthyroidism [70 2 5 84 90] In acute thyrotoxic myopathy there may occur a rapidly developing bulbar palsy and a generalized weakness often ending in early death Thyroidectomy or alleviation of the hyperthyroidism is often followed by recovery [70 74] It has been suggested that the myopathies like some of the neurologic manifestations result from depletion of the body iodine stores and may be improved by the administration of iodine [70] Thyrotoxic periodic paralysis has been reported with cure following thyroidectomy [77] In chronic thyrotoxic myopathy [82 1 0] there is noted symmetrical wasting of the limbs and extremities especially of the proximal portions Coarse muscular fibrillations are observed and the tendon reflexes are diminished

Creatinuria is usually found. Lymphocytic infiltrations of the muscles similar to that seen in myasthenia gravis have been reported, although prostigmine is of no value in treatment. Complete recovery is to be expected after cure of the hyperthyroidism.[78] When myasthenia gravis is present in association with thyrotoxicosis, the former is aided by prostigmine but not by thyroidectomy.[2,80] Myotonia, on the other hand, has been reported in myxedema. Following treatment of the hypothyroidism the signs of the myotonia disappear.[70,81] The most important muscular disorder encountered in hyperthyroidism, however, is that of exophthalmic ophthalmoplegia.[73]

The Eye.—The eye signs may be classified as: 1, the lid signs; 2, the external changes in the lids or eyes; 3, the extraocular palsies and ptoses, and 4, exophthalmos. The lid signs may occur in either diffuse or nodular toxic goiter, as well as in simple nontoxic adenoma, and occasionally in individuals free from thyroid disease. The external changes, which are less common in occurrence than the lid signs, are observed more frequently in diffuse toxic goiter but are also seen in toxic adenoma. The rare extraocular palsies and ptoses are found almost exclusively in diffuse toxic goiter. This is equally true of exophthalmos.[73, 5, 8, 53–56]

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The extraocular palsies are rare, occurring in approximately one third of 1 per cent of patients with diffuse toxic goiter.[70, 5] They may be divided into two groups. The first group consists of single or multiple extraocular palsies associated with exophthalmos and severe thyrotoxicosis. Complete bilateral or unilateral ophthalmoplegia with or without ptosis may occur. Following correction of the hyperthyroidism, the exophthalmos and palsies usually improve. In this group there is a tendency for the muscles of elevation to be impaired first, but any muscle may be involved and different muscles in each eye may become paretic.

The other group of ocular palsies and exophthalmos occurs in association with mild hyperthyroidism and even occasionally without hyperthyroid-

ism The eye manifestations in this group either stay unimproved or as is more generally the case, become worse after treatment of the hyperthyroidism This type of disorder has been variously referred to as *exophthalmic ophthalmoplegia*,[7] *malignant exophthalmos*,[91] *progressive exophthalmos following thyroidectomy*,[59] and *Graves disease with dissociation of thyrotoxicosis and ophthalmopathy* [87]

The genesis of the muscle palsies of the first group has not definitely been determined It has been suggested that they may result from stretching of the extraocular muscles However often a considerable degree of exophthalmos may be present without weakness of any of the muscles Organic changes in the muscles consisting of lymphocytic infiltration and myofibrosis have been described, but these alterations appear to be rare in this group Mulvany s explanation[88] that the fibers undergo wasting with loss of striation, granulation of the sarcoplasm and reduplication of the sarcolemmal nuclei does not appear to be tenable The suggestion that this type of disorder is a manifestation of myasthenia gravis is also not acceptable since prostigmine is without effect on the involved muscles

The syndrome of malignant exophthalmos is an extremely serious one In contrast to the incidence of ordinary exophthalmic goiter it is more common in men than in women and is usually noted in middle life As has been previously mentioned the metabolic manifestations in association with the eye signs may be minimal or absent Indeed the eye symptoms are usually markedly aggravated following subtotal thyroidectomy and to a lesser extent perhaps with the use of the non surgical measures for the treatment of the thyrotoxicosis The exophthalmos may become so marked that closure of the lids is impossible The cornea, being uncovered and unprotected becomes dry and opaque and secondary ulceration may occur In extreme cases the eyes may be lost, and even after enucleation the orbital contents may continue to swell and enlarge

The recognition of this disorder is therefore important Although the presence of the syndrome may become obvious after thyroidectomy has been performed, it is essential that the diagnosis be established prior to that stage The important points are emphasized by Woods [6] as follows 'In the early stages the degree of protrusion may be slight but it usually progresses until it becomes extreme It may be unequal on the two sides Whether the exophthalmos is slight or extreme it is usually accompanied by chemosis swelling of the lids reduction in motility of the eye and disturbances in muscle coordination symptoms of epiphora hyperemia and edema of the conjunctivæ photophobia a sensation of hard resistance when the effort is made to reduce the exophthalmos by pressure on the globes The extraocular paralyses and disturbances of muscle coordination have certain peculiarities especially emphasized by Brain [2] These are the frequent involvement of muscle groups moving the eyes in one plane especially elevation Only rarely is the ophthalmoplegia total usually isolated muscles, or combinations of the recti and obliques being affected The usual thyrotoxic lid signs are absent edema being the main symptom Impairment of vision from optic neuritis is relatively common The pupillary reactions are normal Ptosis is more common than retraction of the lids Frequently marked proliferation beyond the lid margin

is observed According to Means and his associates [4, 87] this syndrome is characterized by only a slight enlargement of the thyroid meager evidences of hyperthyroidism marked ocular symptoms particularly that of orbital edema and a rapid subsidence of the metabolic signs and symptoms following the administration of iodine The eye muscles on pathologic examination exhibit a hypertrophic myositis with interstitial fibrosis edema and lymphocytic infiltration [92, 93] It is probable that the palsies result from the stretching and fibrosis of the muscles It is important to bear in mind that the exophthalmos may occasionally be unilateral In those instances the differentiation from a retro-orbital tumor must be considered X rays of the orbit in the latter instance will show destruction of the bone or foramina whereas in malignant exophthalmos no bony alteration occurs

The pathogenesis of malignant exophthalmos is still a matter of dispute It is apparently not due to the thyroid hormone itself since the disorder is frequently noted in the presence of the euthyroid state and is aggravated concomitantly with the development of the hypothyroid state Moreover it is occasionally helped by the administration of thyroid extract A more commonly accepted explanation is the one which envisages the syndrome as resulting from an overproduction of thyrotropic hormone The administration of thyrotropin to the guinea pig will produce a transient exophthalmos which is more marked in the thyroidectomized animal [93, 100] Marine[94] has suggested that malignant exophthalmos is due to hyperplasia of the orbital contents in contrast to simple edema in the ordinary forms of exophthalmos

Exophthalmos in general is present in over half of all patients with diffuse toxic goiter [75, 76] The degree may be roughly measured by an exophthalmometer In normal subjects the degree of protrusion of the eye when measured by this instrument may be as much as 16 mm but in individuals with myopia may be greater In diffuse toxic goiter the exophthalmometric readings usually vary between 16 and 24 mm When exophthalmos is greater than 24 mm exposure of the cornea and its sequelæ may follow Severe exophthalmos may rarely result in papilledema and optic atrophy Although it has long been taught that the nonmalignant forms of exophthalmos recede following treatment of the hyperthyroidism recent studies would indicate that this is rather infrequent and more often a slight increase probably occurs [96, 97] The apparent clinical improvement in the degree of exophthalmos is probably due to disappearance of the stare

The pathogenesis of exophthalmos has been vigorously pursued by many investigators [75, 76, 103] Although the mechanism involved has not been established recent studies have shed a great deal of light on this problem It is quite generally accepted that in clinical and experimental exophthalmos one or all of the following changes may be encountered hypertrophy of the orbital contents a hypertrophic myositis relaxation of the striated extraocular muscles edema of the orbital contents dilatation of the orbital blood vessels and contraction of the smooth muscles of the orbit or lids It seems unlikely that contraction of the smooth muscles of the orbit plays much of a role in human exophthalmos inasmuch as these muscles are only vestigial remnants It is equally unlikely that either dilatation of the vessels or relaxation of the striated musculature is important Although

hypertrophy of the orbital contents could theoretically produce exophthalmos it is more likely that edema plays a more significant part Smelser[93 100] was able to produce exophthalmos in the guinea pig by the use of thyrotropin The changes were more marked in the thyroidectomized animal and were less following the administration of thyroxin The experimental exophthalmos was *not prevented by extirpation of the cervical sympathetics* nor of Mueller s muscle The orbital contents, with the exception of the lacrimal gland participated in the increase in weight These structures included the fatty connective tissue the extraocular muscles and the dorsal lacrimal gland Histologically the edema was marked and permeated the connective tissue The changes were quite similar to those noted in clinical exophthalmos These findings were subsequently confirmed by Paulson[99] and Aird[94] Rundle and Pochin[304] working with him in material reported that the water content of the fat free tissue was normal but that the fat content of the orbit was markedly increased On the other hand Pochin[305] found results similar to those of Smelser following the injection of pituitary extracts in the guinea pig This problem was further investigated in our laboratory[40] We found an increase in the hexosamine and water content of the orbital tissues in the exophthalmos of guinea pigs treated with thyrotropin This would suggest that the edema of the orbital tissues was probably due to the hydrophilic action of the increased mucoprotein content

A possible explanation for the relatively high incidence of malignant exophthalmos in men may be found in the report of Marine[105] He observed that in the rabbit exophthalmos secondary to thyrotropin administration may be checked by castration and accelerated by testosterone[106] This might also explain the beneficial effects occasionally noted following the use of stilbestrol Dobyns[307] however failed to confirm these observations[297]

The effects of the treatment of the hyperthyroidism on the exophthalmos encountered in Graves disease has been reported by several observers Careful serial measurements would seem to controvert the casual and commonly accepted impression that the exophthalmos of most patients with hyperthyroidism improves following subtotal thyroidectomy The disappearance of lid retraction and associated eye signs conveys this impression of improvement but when careful exophthalmetric readings are employed 75 to 97 per cent of the patients exhibit an increase in protrusion of the eyeballs[78 307] Following x ray treatment of the thyrotoxicosis however Soley[78] found a further progression of the exophthalmos in only 20 per cent Dobyns[307] found that of 11 patients treated with thiouracil 7 showed an increase in exophthalmos of over 1 mm[131 307] Beierwaltes[311] separated his patients with thyrotoxicosis into two groups those with malignant exophthalmos and those with the nonmalignant variety Both groups were treated with thiouracil Of the latter group, only 10 per cent showed progression of the exophthalmos while all 7 patients with malignant exophthalmos showed progression With the use of *radioactive iodine* Soley and his asociates[271] found an increase in exophthalmos of 1 5 mm or more in 30 per cent of 50 patients as compared to 26 per cent following x ray therapy and 50 to 60 per cent following subtotal thyroidectomy

The incidence of malignant exophthalmos is fortunately so uncommon that a large statistical series concerned with the effects of various forms of therapy has not as yet been accumulated. However, the evidence would tend to indicate that malignant exophthalmos probably progresses following any definitive therapy directed at the thyrotoxicosis. Whether the progression is less with the use of radioactive iodine or *x*-ray therapy as compared to subtotal thyroidectomy or treatment with the goitrogens is not certain. Most observers feel, however, that the prognosis is least favorable following subtotal thyroidectomy. In the nonmalignant variety the use of comparatively slow acting therapeutic agents such as *x*-ray therapy, radioactive iodine and the goitrogens seems to be associated with less risk of inducing further exophthalmos than does the use of surgery.

The treatment of malignant exophthalmos is dependent on the stage at which the diagnosis is established. Subtotal thyroidectomy should be avoided and medical measures should be employed to treat the thyrotoxicosis. The administration of thyroid extract, stilbestrol and even more rarely iodine may sometimes arrest or improve the disorder.[127, 128] The rationale for these modes of therapy is based on their supposed ability to inhibit the secretion of thyrotropin and on the part of iodine to inactivate it.[133] Recent studies with the use of cortisone and ACTH suggest that these agents may be beneficial in some instances of exophthalmos.[131] X-ray directed at the hypophysis has been employed with little success[109] but is worth trying. If the eye signs are progressive, various surgical procedures may be necessary to save the eye. These include wedge excision of the conjunctiva, lateral tarsorrhaphy and orbital decompression.[95]

The Relationship of Diabetes Mellitus to Thyrotoxicosis.—The intestinal absorption of carbohydrates, including glucose and galactose, is accelerated by the thyroid hormone.[111] The fasting blood sugar in hyperthyroidism is usually normal, although in some instances it may be slightly increased.[112] Following the oral administration of glucose the blood sugar level at the end of one half hour is higher and subsequently falls more slowly than is observed in normal individuals. At the end of two hours, however, the blood sugar generally returns to a normal level.[113] These abnormalities frequently disappear following thyroidectomy.[114] Mild spontaneous glycosuria may be found in 40 per cent of the patients with diffuse toxic goiter and in 25 per cent of the patients with toxic adenoma.[115] The high postprandial blood sugar level is probably related to the rapid intestinal absorption as well as to the depletion of liver glycogen. This latter results in a form of mild "starvation diabetes," which is unrelated to ordinary diabetes mellitus since the thyroid has no direct effect on intermediary carbohydrate metabolism. Glucose is burned normally in patients with thyrotoxicosis and, indeed, following the ingestion of glucose[112] the respiratory quotient frequently rises more than in normal individuals. It has been demonstrated experimentally that the administration of thyroid extract facilitates the induction of alloxan and pituitary diabetes, as well as the diabetes of the partially depancreatized animal.[110] Thyroidectomy inhibits the development of experimental diabetes.[116] In the experimental animal, diabetes increased by the administration of thyroid extract is characterized by a greater polyuria, a more severe loss of weight and a greater

insulin requirement than in the comparable non-thyroid-treated diabetic animal. From a consideration of these factors, it is therefore, not astonishing that diabetes mellitus is exacerbated by the development of hyperthyroidism.

Although hyperthyroidism is no more frequent in the diabetic than in the non-diabetic, diabetes is twice or even three times as common in patients with hyperthyroidism as in the euthyroid groups. The incidence of diabetes mellitus is greater in patients with toxic adenoma than in those with diffuse toxic goiter. This probably is related to the older age of the former group.[116] When the two diseases are associated, hyperthyroidism precedes the diabetes in 75 per cent of the patients.[119]

Since the fasting and postprandial blood sugar levels are frequently elevated in the patient with thyrotoxicosis, the criteria ordinarily employed for the diagnosis of diabetes mellitus must be altered. The diagnosis of diabetes complicating hyperthyroidism should not be made when the fasting blood sugar level is below 150 mgm. per cent or the maximum rise following the oral administration of glucose is less than 200 mgm. per cent. In thyrotoxicosis the insulin requirement for the control of the diabetes is increased and hypoglycemia when it occurs due to insulin overdosage is usually more severe because of the depletion of liver glycogen. The successful treatment of the hyperthyroidism results in amelioration of the diabetes. The prognosis of the patient with diabetes mellitus with cured hyperthyroidism is no different from that of the ordinary diabetic.[116]

Pregnancy in Relation to Hyperthyroidism.—The thyroid frequently enlarges during pregnancy. Although the basal metabolic rate is normal or slightly depressed during the first six months of gestation, it rises thereafter to somewhat above normal levels at term and then returns rapidly to the pre-pregnancy level.[117] The serum protein bound iodine rises during normal pregnancy to 9 to 11 micrograms per cent in the absence of any evidences of thyrotoxicosis.

Hyperthyroidism is a rather infrequent complication of pregnancy, being encountered in less than 0.2 per cent.[117, 119, 120] Although the administration of thyroid extract is often advocated as a treatment for sterility, the fecundity of patients with hyperthyroidism is not noteworthy. Mussey[118] reported only 42 pregnancies in 7,228 female patients with hyperthyroidism (0.6 per cent). The severity of the hyperthyroidism may increase or decrease during pregnancy, but generally it remains unaltered. The fetus is usually unaffected by the thyrotoxic state of the mother, although 1 case of a cretin born to a hyperthyroid mother has been reported.[121] The incidence of toxemias of pregnancy appears to be somewhat increased in patients with thyrotoxicosis, as does the frequency of spontaneous abortion.[117, 120]

Thyrotoxicosis *per se* does not constitute an indication for interruption of pregnancy. With proper treatment, the hyperthyroid state may be readily controlled and the pregnancy carried to a successful termination. Thyroidectomy is well tolerated and is advocated by most observers, particularly for toxic nodular goiters.[118, 119, 122] The risk attendant upon the surgery in these instances is no greater than that in the non-pregnant hyperthyroid women. In general, where surgery is decided upon it is preferably

performed during the first half of gestation When the diagnosis is established during the second half of pregnancy conservative measures are best employed and surgery deferred until some time after term Today, hyperthyroidism occurring at any stage of pregnancy may be safely and satisfactorily treated with the thiourea derivatives, such as propyl thiouracil [120, 124] With these agents the hyperthyroidism may be well controlled and if the mother is maintained at euthyroid levels no deleterious effects occur in the child [120, 1, 4] In a few instances some thyroidal enlargement has been observed in the newborn infant but this subsides at a later date [122] Breast feeding however should be avoided since the thiourea compounds are excreted in the milk [1, 2]

The use of radioactive iodine is perhaps fraught with some hazard since the fetal thyroid begins to collect iodine during the fourteenth week of life [1, 6] Theoretically, it would therefore be possible to treat the mother with radioactive isotopes before this period with safety to the fetus However at present it is wiser to reserve this form of therapy to the nonpregnant thyrotoxic patients

Pretibial (Localized) Myxedema —Pretibial myxedema is relatively uncommon [127] The lesion occurs almost invariably in patients with severe or malignant exophthalmos The frequency of this disease bears no relationship to the severity of the thyrotoxicosis and indeed often occurs after subtotal thyroidectomy [42, 130, 135, 136] It appears in painless symmetrical patches of variable size but of definite outline on the anterior aspects of the lower half of the legs or the dorsal surfaces of the feet It has been described on the face eyelids and scrotum The skin overlying the lesions is thickened and pigskin like in appearance, and red cyanotic or yellow white in color It does not pit on pressure but will dimple following the local injection of hyaluronidase [41, 128] This would suggest that in part at least the involved area is infiltrated with a mucoproteinous material containing hyaluronic acid The microscopic examination of the lesion reveals the presence of edema and a mucoid degeneration of the corium secondary to a basophilic alteration of the collagen and elastin [134, 135]

The cause of the development of pretibial myxedema is unknown Because of its frequent association with severe exophthalmos it is probable that they have a common underlying mechanism In one instance a high urinary excretion of thyrotropin was noted [42] The treatment for *pretibial myxedema as for severe exophthalmos is unsatisfactory* Occasionally the former will subside spontaneously Any measures which reduce the basal metabolic rate will generally increase the severity of the lesions [4] Iodine thyroid extract and thyroxine however are equally ineffective Estrogens in large doses are sometimes efficacious [4]

Thyroid Storm – The extreme manifestations of thyrotoxicosis are exhibited in the clinical picture known as thyroid storm In this state the overwhelming thyroid intoxication results in marked restlessness delirium tachycardia vomiting and diarrhea dehydration and hyperpyrexia Death frequently ensues In some patients however, the manifestations may be chiefly those of prostration hypotonia and mental apathy, and the temperature may not rise above 101° F

Thyroid storm may follow stress of any sort in a patient with thyrotoxicosis. It is more likely to occur in severe hyperthyroidism. Ordinarily, storm is divided into two main categories referred to as medical and surgical storm. We must emphasize that this is an artificial classification since the clinical manifestations are the same in both groups. Medical storm may occur when the thyrotoxicosis becomes increasingly more severe or when a coincidental infection sets in. Surgical storm may follow thyroidectomy for Graves' disease, or follow any surgical procedure however minor.[143] Following thyroidectomy, storm is more likely to occur if the hyperthyroidism has been inadequately controlled before operation. This is particularly true where the nutrition is poor and there has been a failure to gain weight.[139] The presence of a complicating illness, such as infection or heart disease, further increases the risk.

It has been suggested that part of the picture of storm reflects the effect of thyroxine on the heart and the sensitivity of the thyrotoxic heart to epinephrine-like compounds.[144-146] The cerebral symptoms encountered resemble those observed in anoxic anoxia. The brain in hyperthyroidism appears to be markedly sensitive to anoxia.[147,148]

Waldenstrom[70] has suggested that the acute myeloencephalopathies constitute a variety of apathetic storm which he attributes to depletion of the body iodine stores. Others[140] have postulated that storm is associated with hypothyroxinemia and that both thyrotoxicosis[149] and thyroid storm may be improved following the administration of thyroxine. The evidence for these theses is meager.

The pathologic findings in thyroid storm are minimal apart from those ordinarily encountered in hyperthyroidism. Not infrequently bronchopneumonia is present. Central necrosis and fatty degeneration of the liver were observed in 10 of 11 patients in one series.[145] It is important to note the high incidence of cardiovascular disease in fatal cases of thyroid storm.

The Treatment of Storm.—Thyroid storm usually occurs within four to sixteen hours following subtotal thyroidectomy. In thyrotoxic patients subjected to non-thyroidal surgery, delayed storm may occur as a consequence of a late postoperative complication. Prophylaxis is the single most important measure in reducing the incidence of thyroid storm. Patients with hyperthyroidism, particularly those who are severely toxic, must be treated promptly and vigorously until brought to euthyroid levels. The treatment of thyrotoxicosis is discussed in detail elsewhere but it is important to emphasize at the moment that where radioactive iodine is employed for treatment, it should be followed by lugolization or the administration of propyl thiouracil in order that amelioration of the disease be brought about promptly. In the presence of any infection the administration of antibiotics in adequate dosage is indicated. If surgery is to be carried out, it must await satisfactory control of the hyperthyroid state.

The active treatment of storm is as follows. The patient is promptly placed in an oxygen tent and iodine is administered both orally and intravenously. The former is given in the form of Lugol's solution in a dose of 30 to 45 drops and repeated every four to six hours. In addition 1.0 gram of sodium iodide is given intravenously with similar frequency. As the acute symptoms subside, these medications are decreased in dosage

and administered less often Although propyl thiouracil has been recommended by some in the treatment of thyroid storm it is unlikely that this will have any immediate effect on the crisis but will decrease the amount of circulating thyroid hormone during the period following the acute episode The antibiotics are routinely used even if infection is not obviously present It is desirable to employ wet packs ice bags and other physical measures for decreasing the body temperature and increasing the dissipation of body heat A continuous intravenous drip of 5 per cent glucose in normal saline is administered to combat the dehydration and to increase the glycogen content of the liver Blood transfusions are given if indicated Whole adrenal cortical extract has been suggested in the treatment of storm [11, 184] In one patient with severe thyroid storm whom we have had occasion to treat with adrenal cortical extract the response was dramatic and gratifying Twenty cc of whole adrenal cortical extract is given intravenously and 20 cc administered subcutaneously Ten to 20 cc is then given subcutaneously every hour until improvement is well established when the dosage is gradually reduced Cortisone or ACTH is desirable in preference to whole adrenal cortical extract Fifty milligrams of cortisone or 25 mgm of ACTH is given every six hours day and night Cardiovascular complications must be carefully watched for particularly in the elderly patient Adequate sedation plays an important role in the treatment of storm Enough sedation including morphine paraldehyde, chloral hydrate bromides or barbiturates is employed to control the restlessness and agitation

The Diagnosis of Hyperthyroidism — The diagnosis of hyperthyroidism is usually clinically evident and where it is obscure the laboratory procedures described in the previous chapter should be resorted to [1, 1–160, 182–187]

It is important to differentiate hypermetabolic states without hyperthyroidism from true thyrotoxicosis In the former there is an increase in the basal metabolic rate but none of the clinical manifestations of hyperthyroidism are present Such cases are encountered in 1 disorders of the blood forming organs severe anemia polycythemia leukemia multiple myeloma Hodgkin s disease lymphosarcoma 2 cardiac disorders congestive heart failure some cases of hypertension arteriovenous aneurysm 3 malignant tumors with or without metastases 4 extensive skin diseases with erythroderma and 5 Paget s disease of bone Patients with pheochromocytoma will often manifest an increase in the basal metabolic rate which may be associated with true mild hyperthyroidism or with hypermetabolism without clinical hyperthyroidism Silver and his colleagues[187] studied a group of patients with hypermetabolism and found that the plasma protein bound iodine and the urinary excretion of radioactive iodine were well within the normal range despite elevations of the metabolic rate to levels as high as +91 per cent

Neurocirculatory asthenia must be differentiated from Graves disease The former is characterized by dyspnea precordial pain palpitation exhaustion and an inability to adjust to mental or physical strain There are of course no organic evidences of heart disease Moschcowitz and Bernstein [93] have suggested that neurocirculatory asthenia is a precursor of Graves disease but most observers deny this Where the clinical

differentiation is not certain, the determination of the protein bound iodine or the urinary excretion or uptake of radioactive iodine will separate the two groups.

An important differential diagnosis of Graves' disease is that of thyrotoxicosis due to the ingestion of thyroid extract. *Thyrotoxicosis factitia* is differentiated from true hyperthyroidism by the fact that although the serum protein bound iodine is elevated in both groups, the uptake of radioactive iodine is decreased and its urinary excretion markedly increased in the former state. Following the ingestion of thyroid extract, the functional activity of the thyroid gland is reduced and its behavior in respect to radioactive iodine may approach that of hypothyroidism.

The Treatment of Graves' Disease.—Thyrotoxicosis may be treated either by medical or surgical means. The latter usually consists of subtotal thyroidectomy after the patient has been suitably prepared. The accepted modes of medical treatment include the use of iodine, the thiourea derivatives, or the administration of radioactive iodine.

Although iodine had been employed in the treatment of hyperthyroidism as early as the nineteenth century, its use in this disorder had fallen into disrepute. Plummer[188] in 1923, again suggested its use particularly in the operative management of thyrotoxicosis. From that time until the introduction of the thiourea derivatives it remained the drug of choice both for the preparation of patients for operation and for more prolonged conservative management. The latter use was generally and commendably avoided except in instances of very mild hyperthyroidism and in patients with severe or potentially malignant exophthalmos. The administration of iodine is followed within a few days by beginning subjective and objective improvement. Within ten days to three weeks the tachycardia usually subsides, a gain in weight takes place, the patient becomes much less apprehensive and agitated, and the basal metabolic rate has returned to a reasonable level.[01] During iodine therapy the gland becomes somewhat firmer and histologic section at this time reveals considerable involutionary changes with a decrease in the hyperplasia. The invaginated follicles become rounder and now contain colloid and the lining epithelium becomes flatter.[197] The Golgi apparatus changes in position from a site close to the blood supply to one nearer the follicles. In addition to the decrease in the basal metabolic rate, the blood cholesterol tends to rise and the serum protein bound iodine to fall. However, despite the improvement the patients still appear hyperthyroid and are by no means as well controlled as are those adequately prepared with the thiourea derivatives or after treatment with radioactive iodine or successful surgery. The fall in the basal metabolic rate following the administration of iodine approximates the thyroxine decay curve.[193–195] The maximum response to be expected is a fall of approximately 3 to 4.5 per cent a day.[195, 196] The mechanism by which these effects of iodine are brought about has not been entirely explained. However, some light has been thrown on this subject. Rawson and his coworkers[198, 200] have shown that thyrotropin is inactivated by iodine. Our experimental studies, however, would suggest that iodine prevents the access of thyrotropin to the thyroid, as a result of which thyrotropin appears in increasing amounts in the circulation.[199] Chaikoff

and Wolff have demonstrated that when the level of the inorganic iodine in the blood is elevated there is a decrease in the synthesis of organic iodine although the gland is still capable of trapping inorganic iodine [189–191] It would seem likely therefore, that there occurs a decrease in the conversion of diiodotyrosine to thyroxine [192] It is possible therefore, that iodine exercises its therapeutic effects by either inactivating thyrotropin or preventing its access to the thyroid and by depressing the formation of organic iodine compounds It is important to note that iodine does not affect the circulating thyroid hormone This is evidenced by the fact that it exercises no influence on the symptoms of thyroid intoxication induced by the exogenous administration of thyroid hormone [201]

The prolonged use of iodine in patients with hyperthyroidism may be associated with exacerbations of the disease Following withdrawal of the medication for a period of several weeks to several months the disease again becomes responsive to iodine medication

Thompson and his coworkers demonstrated that the daily minimum completely effective dose of iodine was 6 mgm , or 1 drop of Lugol s solution Amounts less than this induced only a submaximal response, while a larger dosage was of no greater therapeutic efficacy [207] The route of administration is a matter of indifference as is the chemical form in which it is given Thus potassium or sodium iodide elementary iodine Lugol s solution [03] or even diiodotyrosine are equally effective [204]

Rienhoff[149] has reported that the administration of desiccated thyroid extract to patients with thyrotoxicosis will bring about a remission of the symptoms and enable these patients to be safely operated upon Such glands however do not reveal the colloid involution which follows the use of more orthodox forms of iodine [149] It is suggested by this author that the administration of thyroid extract in these instances causes thyroidal atrophy presumably as the result of the inhibition of thyrotropin The amount of iodine in the dosage of thyroid extract employed (0 00132 mgm iodine per grain of thyroid) appears to be too small to exert any true iodine effect The mechanism involved is further elucidated by the observation of Cortell and Rawson [219] who have shown that exogenous thyroxine not only inhibits the formation of thyrotropin but decreases the action of thy rotropin on the thyroid

The question of iodine induced thyrotoxicosis (*Jod Basedow*) is a controversial one Although such cases have been reported especially in areas of endemic goiter abroad in our experience and in the experience of most observers in this country its occurrence is questionable [312 313] The explanation for the development of *Jod Basedow* is based on the concept that a goiter long deprived of iodine when furnished with this substance produces thyroid hormone in excess and clinical thyrotoxicosis results However when iodine prophylaxis for goiter was introduced into the United States no increase in thyrotoxicosis was noted It seems more likely to us that in regions of endemic goiter where iodine deficiency has been long sustained those patients who ordinarily might have toxic goiter would presumably be unable to manufacture the hormone because of iodine lack When iodine is then given for prophylaxis of the goiter the overt evidences of latent hyperthyroidism may then become manifest

Lugol s solution is generally administered in a dosage of 1 to 10 minims 3 times a day This may be given in milk or in orange juice to disguise the taste In some instances, hyperthyroidism can be controlled indefinitely by the administration of Lugol s solution However, such instances are comparatively few and are limited to the relatively mild case of thyrotoxicosis Prior to the introduction of the thiourea derivatives most clinicians employed iodine chiefly for the preoperative preparation of the thyrotoxic patients The introduction of the goitrogens and radioactive iodine into clinical medicine has to a great extent supplanted the use of iodine It is still employed, however in those patients who are prepared for operation with the thiourea derivatives The gland of patients treated with the goitrogens is generally friable and vascular thus increasing the technical difficulties attendant upon its removal The administration of iodine for ten days prior to the operation, in conjunction with the goitrogen will induce involution of the gland and facilitate the surgical procedure[66]

The introduction of the *thiourea* derivatives constituted an important advance in the treatment of hyperthyroidism Following the demonstration by Astwood and his group[207] and by the MacKenzies,[08] of the goitrogenic and hypothyroid inducing potentialities of these drugs the application to clinical hyperthyroidism rapidly followed[206] On the basis of experimental studies on the relative efficacy and toxicity of a large number of compounds thiouracil and thiourea were chosen for use in the earlier investigations in the treatment of clinical thyrotoxicosis[09] Most of these studies centered on the use of thiouracil while relatively few employed thiourea in part perhaps because of the unpleasant breath imparted by the latter It soon became apparent that these drugs in sufficient dosage would invariably reduce the metabolic rate to euthyroid or even hypothyroid levels The chief difficulty however was the relatively high incidence of toxic reactions[3, 29, 35, 13]

Within a few days after beginning of treatment with the thiourea derivatives the patient will note an increase in the sense of well being al though no objective evidence of improvement has yet occurred Within two to four weeks the basal metabolic rate will return to normal levels and most of the clinical manifestations of thyrotoxicosis will subside The tachycardia as a rule persists somewhat longer than the other signs and symptoms The subsidence of the symptoms and the fall in basal metabolic rate usually proceed at a somewhat slower pace than is observed with the use of iodine It is reported that the rate of fall of the basal metabolic rate is approximately one per cent a day although in our experience it has been more rapid In general it may require a period of four to six weeks or even longer to control the disease satisfactorily The response is more rapid in young people in patients with diffuse rather than nodular goiter and in hyperthyroidism of short duration In contrast to the results obtained with iodine, with the thiourea derivatives the basal metabolic rate may be reduced to any desired level This is of great importance where patients are to be prepared for operation All such patients treated with the thiourea compounds may be brought to euthyroid levels and operated upon with the maximum protection against the development of thyroid

storm The administration of iodine before treatment with the goitrogens will delay the effect of the latter

Following the ingestion of the thiourea derivatives the goiter initially enlarges but subsequently often becomes smaller This initial enlargement is a matter of concern in patients with substernal goiters Such patients when treated with these compounds must be carefully watched for the development of respiratory difficulties

The thiourea compounds may be used for the definitive treatment of hyperthyroidism or for the preparation of the patient for subtotal thyroidectomy In the latter instance the drug is administered until euthyroid levels are reached and the criteria for proper surgical preparation are fulfilled This may take from four to six weeks or even longer For the more definitive treatment of hyperthyroidism it has been found that these compounds must be continued for periods of time varying from twelve to eighteen months If treatment is of shorter duration the symptoms usually recur on cessation of therapy often within two to eight weeks[225–32, 37, 243] *The incidence of permanent remissions increases with the more prolonged periods of therapy* Indeed remissions up to four and five years have been reported [46] However the longer the period of observation following cessation of therapy the less the percentage of permanent cure Meulengracht and Kjerulf-Jensen[278] obtained prolonged remissions in 90 per cent of a series of 110 patients Similar results in even larger series were reported by Poate [41] and Frisk [59] However the percentage of prolonged remissions was far less in reports emanating from clinics in this country [274, 276–60, 305] In general the most important factors in the induction of prolonged remissions appear to be the duration of treatment and of even greater importance the degree of control of the hyperthyroidism It is preferable to maintain the patient at slightly hypothyroid levels The concomitant use of iodine appears to lessen the percentage of prolonged remissions [308]

The major disadvantage associated with the use of the thiourea derivatives is the relatively high incidence of toxic reactions The frequency of these reactions varies with the different agents With thiouracil therapy[279, 33–35, 38, 243] toxic reactions are encountered in 6 7 to 18 per cent of the cases These reactions are listed in Table 29 (Curtis and Swenson) In a series of almost 6000 patients treated in various clinics Van Winkle and his associates[279] reported an overall incidence of 13 1 per cent Most of the untoward effects encountered are due not to overdosage with the drug but represent rather examples of hypersensitivity The most important of the toxic reactions encountered are leukopenia and agranulocytosis drug rash and drug fever Leukopenia occurs in approximately 4 per cent of the patients treated with thiouracil of whom one-quarter develop agranulocytosis In addition other patients may suddenly develop agranulocytosis without previous evidence of leukopenia It must be emphasized however that leukopenia does not necessarily herald agranulocytosis since the leukopenia frequently disappears despite continuation of therapy Agranulocytosis usually occurs between the fourth to eighth weeks of treatment but instances have been reported after as short a period as seven days of treatment and as long a time as a year of therapy In one

instance, agranulocytosis occurred six months after cessation of treatment. Drug fever is encountered in 2.7 per cent and dermatitis in 3.3 per cent. The fever almost invariably occurs on the tenth to the eighteenth day of treatment. When the drug is withdrawn, the temperature promptly falls, but rises again if it is readministered. Other less common toxic effects include lymphadenopathy, swelling of the salivary glands, arthritis and rarely periarteritis nodosa. Jaundice and liver damage have been observed chiefly in association with agranulocytosis.

Table 23.—Toxic Reactions Following the Use of Goitrogens (Curtis Swenson)

Bone Marrow Effects	*Cardiovascular Effects*	*Central Nervous System Effects*	*Gastrointestinal Effects*
Agranulocytosis	Heart block	Coma	Nausea
Anemia	ECG changes	Confusion states	Vomiting
Granulocytopenia	Periarteritis Nodosa	Delusions	Diarrhea
Leukopenia	Pericarditis	Dizziness	Abdominal pain
Neutropenia	Purpura	Headache	
Thrombocytopenia	Flushing	Loss of ankle jerks	
		Loss of vibratory sense	
		Nausea	
		Vomiting	
		Persecution complexes	
		Various psychoses	

Liver Effects	*Lymphatic Effects*	*Miscellaneous Effects*	*Ophthalmic Effects*
Acute yellow atrophy	Enlarged lymph nodes	Arthritis	Chemosis
Degeneration of liver lobules	Enlarged salivary nodes	Choking	Conjunctivitis
		Dryness of the mouth	
Hepatitis	Leg edema	Faintness	
Jaundice	Myxedema	Hematuria	Increased exophthalmos
		Fever	
	Enlargement of Thymus	Joint pains	Photophobia
		Muscular pains	
		Pharyngitis	
		Thirst	

Effects on the Skin

Leukoderma	Macular rashes
Maculopapular rashes	Morbilliform rashes
Purpura	Pruritus
Urticaria	Urticaria with pruritus
Scleroderma	Painful subcutaneous nodules

Thiouracil is administered in a dosage of 400 mgm. a day until the basal metabolic rate falls to within the normal range. It is then given in a maintenance dosage which varies in different patients from 50 to 200 mgm. daily. The drug is best given in divided doses 3 times a day and blood counts should be performed twice a week.

Thiourea in large doses has been found to be effective but unfortunately frequently gives rise to toxic side effects identical with those observed with thiouracil. However, by employing iodine in conjunction with this compound, Danowski and his associates[26, 31] were able to employ smaller amounts of this drug. With the combined therapy, they encountered only 2 instances of toxic reactions, that of drug fever, in a series of over 100 patients. Unfortunately, the hyperthyroidism was not controlled in all instances. It is possible therefore that thiourea may be better

tolerated than thiouracil but it is hardly the ideal goitrogen Thiourea is usually administered in a dosage of 1 to 3 grams a day When given in conjunction with iodine Danowski and his group[226-231] obtained satisfactory results with 200 mgm a day

Methyl thiouracil has been extensively used for the treatment of thyrotoxicosis [38, 48, 64, 300] It is twice as active as thiouracil and can be given in doses of 200 to 400 mgm a day Bartels [46] reports toxic manifestations in 9 per cent of the patients of whom 1 5 per cent developed agranulocytosis This complication occurred in 2 of 18 patients treated in our clinic In addition in 3 others severe toxic reactions necessitated cessation of therapy The results described by other investigators have been somewhat more favorable [38, 48, 64, 300] The clinical effects are perhaps more rapidly induced with methyl thiouracil The usual precautionary measures must be employed with this agent as with the other goitrogens Blood studies with particular emphasis on the white blood cell count and differential studies should be done twice a week

Propyl thiouracil in our experience has been perhaps the most satisfactory of the presently available thiourea compounds for the treatment of hyperthyroidism The incidence of toxic reactions is approximately 2 per cent [34, 39, 247, 248-250] Agranulocytosis is uncommon but does occur Bartels[246] reports the incidence of this complication to be 0 6 per cent The drug is usually administered in a dosage of 300 to 350 mgm a day in 3 divided doses and progressively reduced in amount when the basal metabolic rate returns to normal levels The usual maintenance dose varies from 50 *to 150 mgm a day White blood cell counts and differential studies should* be performed twice a week

Other antithyroid compounds are now in the process of being tested These include mercaptoimidazole and methylmercaptoimidazole and some iodinated thiouracils[-51] A good many other thiourea and thiouracil preparations including thiobarbital tetramethyl thiourea diethyl thiourea 5 6-dimethyl thiouracil 2 thio-4 5-dimethyl-6 methylethyl pyrimidine have been employed clinically but have not been found to be entirely satisfactory generally because of the frequency and severity of the toxic reactions [30, 43] Table 30 lists the relative effectiveness of some of these compounds [308]

Aminothiazol introduced by the French for the treatment of thyrotoxicosis [94] was found to be unsatisfactory by English and American observers because of the frequency of toxic reactions [24, 96, 300] Paraxanthine [61] and and para aminobenzoic acid[-63] have been advocated for the treatment of hyperthyroidism These agents however were found to be clinically ineffective by Williams[-62, 308]

The results of the surgical treatment of hyperthyroidism are excellent in the properly prepared patient Following preparation with the goitrogens with or without the adjuvant use of iodine the mortality rate need not exceed 0 24 per cent [3] Pemberton [2] reported 611 patients with diffuse toxic goiter who were subjected to subtotal thyroidectomy without any fatalities Of 496 cases of toxic nodular goiter operated upon 2 patients died The combined mortality rate of the two groups was 0 18 per cent Permanent cure is effected in 95 per cent of the patients [53] In 1000 cases

operated upon since 1943 and reported by Cattell[293] the complications encountered were as follows: postoperative hemorrhage 2.7 per cent, tracheotomy 1.3 per cent, hypothyroidism 4.5 per cent, tetany 1.5 per cent, recurrent laryngeal nerve injury 1.0 per cent, recurrence of hyperthyroidism 2.1 per cent, total mortality rate 0.2 per cent. It is interesting to note the decrease in mortality from that of the iodine period, 1923 to 1943, during which time 1 per cent of the patients died postoperatively. The results obtained with surgery are of course in good part dependent on the competence of the surgeon. The recurrence rate of hyperthyroidism after subtotal thyroidectomy has been reported to vary from 2.3 to 17.5 per cent.[295-298]

TABLE 30.—RELATIVE EFFECTIVENESS OF ANTITHYROID AGENTS USED IN THE TREATMENT OF HYPERTHYROIDISM (TAKEN FROM ASTWOOD[308])

Compound	*Relative Effectiveness in Hyperthyroidism*	*Effectiveness in Human Subjects Radioactive Iodine Test*
6-methyl thiouracil	>1 to 3	2
6-ethyl thiouracil	5	1
6 Cyclopropyl thiouracil	2	1
6 n propyl thiouracil	1 to 5	0.75
6 n Butyl thiouracil		0.75
6-Benzyl thiouracil		0.75
Thiobarbital	2 to 12	2
Thiourea	1	1
Diethyl thiourea	<1	
Tetramethyl thiourea	1	
Mercaptoimidazol	5 to 10	10
Mercaptobenzimidazole	0.75	2.5
Aminothiazole	<1	2.5
2 mercapto-5 amino 1 3 4 thiadiazole		2
Sulfadiazine		<0.05
para aminobenzoic acid	<0.1 to 1	

* Based on a comparison with thiouracil as a standard, the latter being represented as one.

The proper preparation of the patient for operation is as important and integral a part of the treatment as is the subsequent surgical procedure. Proper preoperative preparation requires that the patient be brought to euthyroid levels, that he gain weight, and that the tachycardia subside. The period of preparation varies considerably with the patient. Haste must never be a consideration and the duration of the preoperative treatment may vary from four weeks to several months. Most effective preparation is obtained with the use of one of the goitrogens. In addition, Lugol's solution is added to the regimen for ten days before the operation. Both agents are continued for one week after the operation. The use of ample sedation to allay the anxieties and fears of the patient, as well as the ingestion of a high calorie diet augmented with orally administered members of the vitamin B Complex, are recommended as part of the preparatory regimen.

Postoperative hypothyroidism or myxedema is easily treated. It is important to be cognizant of the early signs, such as a sensation of coldness

aches and pains, fatigue and listlessness The administration of thyroid extract will restore these patients to euthyroidism

Postoperative hemorrhage may occur even with the most meticulous and competent surgeon The symptoms suggesting hemorrhage in the wound are the presence of a mass and the sudden onset of dyspnea The suspicion of the diagnosis warrants immediate re-exploration of the neck and ligature of the bleeding vessel Tracheotomy may occasionally be necessary

Recurrent nerve injury results in the loss of voice or hoarseness At first a flaccid paralysis of the vocal cord is observed and the position of the affected cord is cadaveric Later spasticity occurs and the cord assumes a midline position It is for this reason that bilateral nerve injury results in respiratory obstruction At the Lahey Clinic exposure of the recurrent laryngeals during the operative procedure reduced the incidence of injury to these nerves by two-thirds [24] With unilateral recurrent nerve injury the voice may improve over a period of three to twelve weeks If the injury is due to edema full recovery generally takes place In patients with bilateral nerve injury respiratory obstruction does not occur for several hours Tracheotomy should be performed as soon as respiratory difficulties become evident At a later date re-exploration of the neck is indicated in an attempt to correct the cause of the nerve injury Ultimately if no improvement is afforded by the secondary operation a plastic operation on the cords may provide an adequate airway [13]

The use of x ray therapy was for the most part abandoned following the introduction of iodine in the preoperative treatment of hyperthyroidism A considerable percentage of patients with hyperthyroidism can be cured by x ray treatment [75] Soley and Stone [8] in a series of 43 patients reported cure in more than one-half following x ray treatment Another 20 per cent were improved [8] In addition they claimed that radiation therapy had less of a deleterious effect on exophthalmos than did surgery Much earlier Means and Holmes[279] had reported cure in one-third of their patients and improvement in another third Pfahler[277] collected several thousand cases from the literature and stated that cure was obtained in approximately two-thirds of the group and improvement in another 25 per cent

Radioactive iodine has proven to be an effective form of treatment for hyperthyroidism and it is possible that in most instances it may replace the other forms of therapy available today The isotope employed is I_{131} and the dosage is dependent on 1 the percentage uptake of iodine by the gland and 2 the size of the gland The former may be estimated by tracer studies The latter obviously can be calculated only grossly As a guide it is perhaps desirable to remember that a thyroid gland which is just barely palpable weighs approximately 25 to 30 grams It is not by any means certain that the same dose of irradiation will produce the same degree of destruction in the thyroid glands of different individuals Consequently any calculations based on these factors constitute only a rough approximation Hames and his associates employ a formula for calculating the dosage required [72]

$$\frac{\text{(Estimated thyroid weight) (200-250 microcuries per gram)} \times 100}{\text{Percentage of } I_{131} \text{ tracer collected by thyroid}} = \text{desired dosage in microcuries.}$$

Similar methods of calculation are employed by other investigators [2,3,274,81,63]. At the Mount Sinai Hospital an attempt is made to deliver 10 000 roentgen units or 80 microcuries per gram of thyroid tissue [81]. Werner and his associates[273] found that a dosage of 100 microcuries per gram of thyroid gland is adequate for the treatment of hyperthyroidism. It is interesting to note that satisfactory results have been obtained with amounts of I_{131} which vary from 23 to 574 microcuries per gram of gland [67].

In 288 patients collected from the literature and reported by Soley and Foreman,[67] the total dosage employed varied from 3 to 10.9 millicuries. However, the millicurie standards may vary in different laboratories. Of this group, satisfactory results were obtained in 83 per cent and fair results in 10 per cent.

Feitelberg and his coworkers [81] reported the results obtained in 184 patients with hyperthyroidism treated with radioactive iodine. The average total amount employed for the initial treatment was 8.2 millicuries. Of this group, 132 patients required one treatment, 43 required a second dose and 9 patients required 3 treatments. Almost 100 per cent of the patients were cured of the disease. Improvement is gradual but an appreciable change is usually not evident in less than three or four weeks after the administration of the radioactive iodine. Approximately four to twelve weeks elapse after treatment before maximum therapeutic results are evident. If at the end of this period satisfactory results are not achieved a second dose of radioactive iodine is administered. Occasionally during the first two weeks after treatment an exacerbation of the symptoms and a rise in the serum protein bound iodine is noted. This may be due to destruction of the gland and the outpouring of the preformed thyroid hormone [267,273]. At times cough and soreness of the throat may occur. Radiation sickness is rare with I_{131} [67]. Permanent hypothyroidism or myxedema is reported in 5 to 7 per cent [67,81]. Transient hypothyroidism occurs in an additional small number.

Soley, Miller and Foreman[271] found an increase in the measured exophthalmos in 30 per cent of patients treated with radioactive iodine as compared to an incidence of 26 per cent following x ray therapy and 40 to 50 per cent after subtotal thyroidectomy. In 2 patients with malignant exophthalmos treated with radioactive iodine at the Mount Sinai Hospital progression of the eye signs continued.

The question has been raised as to whether radioactive iodine may eventually exercise a carcinogenic effect. It is for that reason that many clinics restrict the use of this agent to patients over forty years of age. No proof that this can occur has been produced to date and indeed no such development has been observed following x ray therapy for thyrotoxicosis.

Radioactive iodine is most effective in the treatment of diffuse toxic goiter. Because of the possibility of the presence of an underlying malignant neoplasm, patients with mildly toxic nodular goiter are preferably subjected to surgery. However the nodular goiters do respond to radio

active iodine although they require a somewhat larger dosage and a longer period of time for maximum improvement

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Chapter 27

TUMORS OF THE THYROID GLAND

NODULAR GOITER. BENIGN AND MALIGNANT THYROID TUMORS. ENDEMIC AND SPORADIC (COLLOID) GOITER. THYROGLOSSAL DUCT CYSTS. AMYLOID GOITER.

Nodular Goiter.—The enlarged nodular thyroid gland may be the seat of hyperactivity or it may cause pressure symptoms because of its size and location but its major significance is concerned with the possible presence of malignancy. Occasionally a carcinoma of the thyroid is readily recognized clinically. Often it is suspected because of the hard quality of the mass in question. Generally, however, the solitary nodule and the multinodular goiter present no particularly distinguishing features to suggest malignancy other than its statistical incidence. The incidence of malignancy of the thyroid differs in the various forms of goiter. In general it is much more common in the nodular goiters than in the smooth and diffusely enlarged glands. Similarly, it is more frequent in the nontoxic nodular goiters than in the toxic ones, and finally it is considerably more common in the thyroids with solitary nodules than in the multinodular goiters.

The over-all incidence of carcinoma in nodular goiter varies approximately from 4 to 10 per cent. This group includes the multiple and solitary nodules and the toxic and nontoxic groups. Thus Brenizer and McKnight[1] report 2,324 cases of combined toxic and nontoxic nodular goiter, 4 per cent of whom were proven to have carcinoma of the thyroid. Of 1,135 similar cases reported by Horn and his group,[2] 6.3 per cent had carcinoma. Crile[3] described 537 cases with an incidence of carcinoma of 5.6 per cent. Ward[4,5] reported 3,539 cases, and Cole and his coworkers[6] 663 cases, with an incidence of malignancy respectively of 4.8 and 7.2 per cent. Cope and his group[7] reported that of 1,109 nodular goiters operated upon 10.1 per cent were found to have malignant lesions. When the group of cases with nodular goiter is subdivided into toxic and nontoxic divisions, it is obvious that the incidence of malignancy is considerably greater in the nontoxic group. Thus, in the patients cited by Horn and his group[2] above, of the 1,135 cases 637 were instances of nontoxic nodular goiter and 9.8 per cent of this group had carcinoma, while of the 498 patients with toxic nodular goiter only 1.8 per cent had carcinoma. Similarly, in the patients reported by Cole and his group,[6] of 378 cases of toxic nodular goiter only 1 per cent had carcinoma, in contrast to 17.15 per cent of 285 patients with nontoxic nodular goiter. Of 263 patients with toxic nodular goiter reported by Crile,[3] none had carcinoma, while 10.9 per cent of the nontoxic group were thus afflicted. Thus, carcinoma of the thyroid occurs most infrequently in patients with nodular goiters who manifest evidence of hyperthyroidism. But the point to be emphasized is that it does occur and its possibility cannot be entirely

excluded on the basis of the presence of thyroid hyperactivity. Carcinoma of the thyroid may occur in patients with Graves' disease with a diffusely and smoothly enlarged gland. Its incidence in this group is exceedingly low. Ward[4] found only 1 such case in 1900 patients with diffuse toxic goiter but Pemberton and Black[5] found 14 cases in 3500 patients, an incidence of 0.4 per cent. Cole and his group[6] found an incidence of 0.2 per cent in 517 patients.

The greatest incidence of carcinoma of the thyroid is to be found in patients with solitary nodular goiters. When the group of nontoxic nodular goiter is further subdivided into those with solitary nodules and those with multiple nodules, it is found that the frequency of carcinoma in nodular goiters is due in greater part to the great frequency with which it is encountered in the goiters with solitary nodules. Thus, in Crile's group[3] of 271 cases of nodular nontoxic goiter, 3.4 per cent of the multinodular goiters had carcinoma in contrast to 24.5 per cent in the cases with solitary nodules. In the 285 patients with nontoxic nodular goiter reported by Cole and his group,[6] 24.4 per cent of the cases with solitary thyroid nodules and 9.8 per cent of the group with multiple nodules had carcinoma. Of the patients with solitary nodules reported by Ward,[4,5] 15.6 per cent had carcinoma in contrast to 4.8 per cent in the entire group of nodular goiters. Nineteen per cent of the 156 patients with solitary nodules reported by Cope and his group[7] showed malignant changes.

On the basis of these studies we would summarize the incidence of malignancy of the thyroid essentially as follows:

1. Carcinoma of the thyroid may occur probably coincidentally in patients with diffuse toxic goiter (Graves' disease). The incidence is exceedingly low, in general being less than 0.5 per cent.
2. Carcinoma of the thyroid may occur in patients with toxic nodular goiter. Its incidence in this group is greater than that in the toxic diffuse goiter but is still low, and in general is less than 2 per cent.
3. The incidence of carcinoma of the thyroid in patients with multiple nodular nontoxic goiter varies in the literature from 3 to 10 per cent.
4. The incidence of carcinoma of the thyroid in patients with a solitary nontoxic nodule varies in the literature from 15 to 25 per cent.
5. On the basis of very limited reports, the incidence of carcinoma in children with nontoxic nodular goiters is greater than 19 per cent.[4,9]
6. The incidence of carcinoma of the thyroid in males with nodular goiters is considerably greater than that of females.[4,5,6]

In evaluating the significance of the data cited above it must be remembered that these statistics are based on a highly selected group of patients. The cases reported represent patients who have been operated upon and, therefore, have finally arrived at this stage through a rather extensive screening process. By far and large, although not always so, they have been subjected to surgery for some compelling reason other than a prophylactic one. In most instances the mass in the neck had grown or produced uncomfortable symptoms or aroused the suspicions of the referring physician. In this sense, such patients represent a selected population and the statistical conclusions achieved from their study are not necessarily representative of the group with nodular goiter as a whole.

Not all patients with masses in the neck particularly the small solitary nodules seek medical advice and by no means are they always urged to be operated upon When the nodule is small and soft, it is a common practice to defer operation for observation Consequently the ostensibly alarming frequency with which carcinoma of the thyroid occurs in the solitary nodule for example must be viewed in this perspective Indiscriminate prophylactic surgery could prove to be a herculean undertaking in view of the fact that in endemic areas the incidence of nodular goiter in autopsy material may be as high as 80 per cent [10] Even in the New England nonendemic region 8 2 per cent of routine autopsy material revealed the presence of thyroid nodules 1 centimeter or more in size [11] Such nodules are clinically palpable Rogers Asper and Williams[12] approached this problem somewhat differently They reviewed the records of patients with goiter admitted to 3 large eastern general hospitals There were 3 221 such patients with goiter admitted to these hospitals A pathologic diagnosis of malignant neoplasm of the thyroid gland was made in 64 cases or 1 99 per cent The histologic study was obtained either on autopsy or from surgical material VanderLaan[13] reviewed the autopsy material in 3 Boston hospitals and found that carcinoma of the thyroid was a rare cause of death

Autopsy material is as unsatisfactory a basis for statistical study of carcinoma of the thyroid as is surgical material Patients with carcinoma of the thyroid do not necessarily die in hospitals and hence the unusually low statistical incidence of thyroid malignancy in this group is as misleading as the excessive incidence in the group of patients operated upon

The problem of the incidence of carcinoma of the thyroid is a difficult one and it propounds a dilemma which cannot be readily resolved Even if the disease is not as common as the surgeons would have us believe it occurs with great enough frequency to warrant anxiety and careful judgment In general it is a wise policy to regard solitary thyroid nodules with suspicion regardless of the age of the individual Malignant changes are even more common in such nodules in young people than they are in the older age groups Indeed in nonendemic regions solitary nodules are rare in people under the age of thirty and when present should be regarded most suspiciously [14] Single nodules therefore should in most cases be removed particularly if they have grown in size and increased in firmness The propriety of the prophylactic removal of multinodular goiters is more questionable Since in the diffusely nodular goiter the entire gland is generally the seat of nodules true prophylaxis should call for total thyroidectomy This is a procedure which is not lightly decided upon and usually therefore partial or subtotal thyroidectomies are performed Under these circumstances only partial protection is afforded and malignant changes may develop in the nodular tissue left behind [3] Where the gland increases rapidly in size or produces pressure symptoms or when a certain portion of the gland becomes larger harder and perhaps more adherent surgery should promptly be resorted to

Benign Tumors of the Thyroid Gland —The histology of the normal thyroid gland varies with the age of the individual Rice [15] in a study of 500 thyroids obtained at autopsy from individuals whose thyroid glands

were ostensibly normal clinically found considerable variations among the different age groups The patients studied varied from birth to the age of eighty years The gland is tiny at birth weighing approximately 1 5 grams and reaches a maximum weight of approximately 30 grams in early adult life From this point on it gradually decreases in size to an average weight of 20 grams at the age of eighty During the first few years of life the follicles in the gland are small round and of fairly even size and lined by cuboidal epithelium In the older age group the histologic appearance of the gland tends to revert back again to the infant type During both infancy and old age there is a considerable amount of interacinar epithelium, which practically disappears during early adulthood

The structure of the thyroid gland is influenced to a considerable degree by various environmental factors, such as diet and by the usual physiologic stresses [16] This is particularly noticeable during puberty when the physiologic needs for the thyroid hormone are increased Under such circumstances, the development of hypertrophy and hyperplasia of the gland is common and is especially evident in girls of this age group Iodine lack such as occurs in endemic areas intensifies this problem The thyroid hormone requirements vary from period to period and result in concomitant hyperplastic and involutionary changes Thus within a given period of time the gland may develop from a normal structure to a hypertrophied and hyperplastic one followed by involutionary changes either to the normal state again or by hyperinvolution to the stage of that of the colloid goiter [15] Marine has suggested that recurrent thyroid hyperplasia may eventually result in exhaustion atrophy [16 17] This is most clearly seen in the iodine deficiency states where a normal thyroid may become hypertrophied and hyperplastic in an effort to manufacture enough thyroid hormone in the presence of iodine lack and may eventually result in exhaustion atrophy on the one hand or a colloid goiter on the other Actually the same thyroid may show varying degrees of involution and hyperinvolution A previously hyperplastic gland may have involuted areas of a perfectly normal thyroid structure and in other regions of the same gland hyperinvolution may result in small colloid nodules [18 19] The physiologic and environmental variations in hormone requirements which occur with the onset of puberty and thereafter account for the fact that innocent thyroid nodules are uncommon before this period and progressively increase in number and frequency thereafter as the individual grows older

The *involutionary nodule* constitutes the largest percentage of the nodules found in the single or multiple nodular goiter This type of nodule was found in approximately 40 per cent of a group of 96 patients with single nodules in the thyroid reported by Soley Lindsay and Dailey [6] Although colloid goiters are generally diffusely enlarged they are frequently irregular and nodular On histologic examination there are many normal areas as well as many acini greatly dilated lined with a flat epithelium and filled with dense colloid These represent involuted acini In addition there are scattered through such a colloid goiter many small areas of hyperplastic thyroid tissue Involutionary nodules are therefore the common type of nodules found in nontoxic nodular goiter and indeed they may be present singly or in numbers in otherwise normal glands These nodules

represent involution or hyperinvolution of one or several thyroid lobules which are surrounded by thickened fibrous tissue serving to encapsulate the nodule. On microscopic examination these nodules are seen to consist of large distended colloid follicles lined with a flat epithelium and encapsulated by fibrous tissue. Incorporated within the nodular area may be found small nests of hypertrophied thyroid tissue. The involutionary nodule is frequently prone to bleeding with a sudden increase in size and the development of pain and tenderness. Subsequent cystic degeneration and calcification are not infrequently observed. In the areas immediately surrounding the involutionary nodules the acini are flattened and compressed. Wegelin[10] refers to the involutionary nodule as *struma nodosa macro follicularis* or macrofollicular nodules. This type of nodule in view of the nature of its development can hardly be classified as a true adenoma.

Other benign nodules found in the thyroid are classified by Wegelin[10] as follows: *Struma nodosa trabecularis* or trabecular adenoma. This adenoma consists of cords of cells with ill-defined cell borders closely packed together and resembling the least differentiated embryonal fetal thyroid. The *struma nodosa tubularis* or tubular adenoma consists of cell cords arranged in tubular form and somewhat less closely packed than the trabecular adenoma. The tubular adenoma is only slightly more mature in structure than the trabecular one. Both tumors are of low functional level as is evidenced by the fact that they take up radioactive iodine poorly[15] and both are frequently referred to as *embryonal* or *fetal* adenomas. The *struma nodosa micro follicularis* or the microfollicular adenoma resembles the thyroid of a newborn infant in appearance.[15] It is made up of small round follicles closely packed together containing little or no colloid and lined by cuboidal epithelium. This is a much more differentiated tumor than the ones described above and according to Rawson[1] is capable of concentrating considerable amounts of radioactive iodine and indeed of producing hyperthyroidism. This tumor is also sometimes referred to as a fetal adenoma. The *struma nodosa micro et macro follicularis* or the micro and macro-follicular adenoma is made up of many small follicles lined with cuboidal epithelium and many large ones containing normal appearing colloid and lined with a flat to low cuboidal epithelium. The acini are widely separated by hyaline or fibrous material. These tumors take up radioactive iodine in amounts approximating that of normal thyroid tissue.[15] This tumor is sometimes referred to as a mixed adenoma.[1] The *papillary cystadenoma* is a benign tumor but it has been known on occasion to show blood vessel invasion and under such circumstances could be considered potentially malignant.[1] These tumors according to Wegelin[10] and Rawson[15] result from diffuse or local hyperplastic changes. On microscopic examination they are seen to consist of hyperplasia of the lining epithelium of a cystic adenoma. The tumor is well encapsulated.

It must be emphasized that the classification of benign tumors outlined above is by no means absolute but is rather one of convenience. There is such considerable histologic overlapping and variation that no available classification today is entirely satisfactory. In 18 per cent of the cases studied by Soley and his coworkers[9] single nodules observed in the thyroid had to be grouped as unclassified since their histologic structure resembled

both that of adenoma with varying degrees of acinar differentiation and that of involutionary nodules with some residual epithelial proliferation. Of importance, however, is the fact that most nodules in the thyroid are benign. Ninety to 97 per cent of multiple nodular goiters are benign goiters and 75 to 85 per cent of solitary nodules are benign. Of the benign solitary nodules approximately 40 per cent are involutionary nodules and therefore probably do not represent new growths, while another 20 per cent represent adenomas of one type or another. The remaining group of nodules although benign are difficult to classify.

The uptake of radioactive iodine by the benign tumors varies essentially with the degree of differentiation of the tumor. According to Rawson and his coworkers[3] the highly undifferentiated tumors such as the trabecular and tubular adenomas, collect only minimal amounts of the radioactive isotope. Those showing early differentiation such as the microfollicular adenoma, show a greater avidity for radioactive iodine than do the highly undifferentiated tumors. Actually, the uptake of the isotope by these tumors was in several instances greater than that of the uninvolved surrounding tissue, although in others it was less. Tumors showing intermediate degrees of differentiation such as the micro and macro-follicular adenomas take up varying degrees of radioactive iodine. Some of these tumors take up less radioactive isotope than does the surrounding normal thyroid tissue and others as much or more. The involutionary nodules or colloid adenomas in general take up somewhat less iodine than does normal thyroid tissue. Hyperplastic benign tumors of a well-differentiated cell type may take up more radioactive iodine than does normal thyroid tissue and may cause clinical manifestations of hyperthyroidism.

Malignant Tumors of the Thyroid.—In a comparatively small percentage of cases the pathologic recognition of malignant thyroid tumors may be difficult. This is in part due to the fact that the criteria for thyroid malignancy are not as well defined as they are for other organs and in part because the clinical course may be inconsistent with the histologic findings. There is no difference of opinion concerning the malignant character of 1 papillary adenocarcinomas 2 follicular and alveolar carcinomas 3 Hurthle cell adenocarcinomas 4 solid adenocarcinomas 5 small and giant cell carcinomas 6 epidermoid carcinomas and 7 the sarcomas such as the fibro- and lympho sarcomas.[2] It is important to emphasize that these tumors may not be present in a pure histologic form but rather that considerable pleomorphism occurs.[16] Nevertheless their general malignant character is readily recognizable. The degree of malignancy varies with the different types of tumor. Warren classified the papillary, alveolar and Hurthle cell adenocarcinomas as tumors of moderate malignancy, while the small and giant cell carcinomas, the epidermoid carcinomas and the fibro- and lympho sarcomas are classed as highly malignant tumors.

In addition to these definitely malignant tumors there are ostensibly benign thyroid tumors which may sometimes show blood vessel invasion. In this category are the benign thyroid adenomas and the papillary cyst adenoma. Of 1,114 thyroid adenomas removed at operation, Warren[21] found 5 instances of blood vessel invasion in 67 cases of trabecular and tubular adenomata and in 28 of 505 patients with microfollicular adenomata

No instances of blood vessel invasion were found among the cases of colloid adenomata. Actually, less than 3 per cent of all adenomata show blood vessel invasion. Ten per cent of the group showing this histologic abnormality, however, subsequently developed definite clinical evidence of malignancy.[4] Benign tumors of the thyroid, therefore, which have invaded local blood vessels may subsequently become malignant.

Papillary Adenocarcinomas. — These tumors are the least malignant and most common of all thyroid carcinomas. They tend to occur in the younger age groups and are frequent during the fourth and fifth decades of life. This is the tumor which is most often seen in young people with carcinoma of the thyroid. Of 25 patients twenty-one years of age or younger with thyroid malignancy reported by Frazell and Foote,[25] 20 had papillary adenocarcinomas. This type of tumor is approximately twice as common in females as in males.[25,4] The papillary adenocarcinomas are generally small in size, varying from a few millimeters to 4 centimeters, but occasionally are considerably larger.[25] A preexisting goiter is present in approximately three-quarters of the patients according to the report of Frazell and Foote.[25]

Cervical lymph node metastases are common with this tumor, and indeed not infrequently the metastatic disease in the nodes may obscure the presence of a minute primary tumor in the thyroid lobe on the affected side. Since the primary thyroid tumor may be small and inconspicuous, it was believed for a long time that the thyroid tissue present in the lateral cervical regions arose from thyroid anlagen and this hence was referred to as *lateral aberrant thyroid tumors*. There was a good deal of difference of opinion as to whether these cervical masses were actually malignant. During the course of the years, however, the malignant character of these masses became more generally appreciated. Eberts[7] originally suggested that these cervical tumors were metastatic, and Pemberton[8] and King and Pemberton[9] have emphasized that the latent cervical tumors represent metastatic lymph nodes secondary to a primary carcinoma of the corresponding thyroid lobe. In a review of 51 such cases these authors found that the tissue in the cervical regions was histologically indistinguishable from that of a frank papillary adenocarcinoma of the thyroid gland, and in every case in which information was available a papillary adenocarcinoma was present in the corresponding thyroid lobe. In many of their patients lymph node architecture was still evident around the papillary areas. In general, the lateral neck masses were found at those sites where lymph nodes are normally present. In a review of 112 cases of papillary adenocarcinoma of the thyroid reported by Black,[4] the conclusions of King and Pemberton were thoroughly substantiated. In 44 of these cases the cervical lymph nodes were involved and in 16 patients of this group the lesions clinically were typical of "*lateral aberrant thyroid tumors*." In every instance a primary tumor was found in the lobe of the thyroid on the affected side. Crile[3] found a primary tumor in the corresponding thyroid lobe in every one of 16 consecutive cases operated upon. Bilateral thyroid tumors were found in 4 instances.

It would seem, therefore, that *lateral aberrant thyroid tumors* probably represent metastatic lesions from a primary papillary adenocarcinoma

of the thyroid. The thyroid papillary carcinoma may also produce more typical cervical lymph node metastasis and indeed may metastasize more distantly. Bilateral cervical lymph node involvement and mediastinal, osseous, intraocular, and intracranial metastases have been reported.[1-5]

Papillary adenocarcinoma of the thyroid frequently pursues an extremely prolonged clinical course. Patients commonly survive for from ten to twenty-five years despite the recurrent cervical lymph node metastases and even in the presence of more distant metastases,[2-] and eventually die from totally unrelated causes. However, not all patients run such an essentially benign course, and death may result from local invasion of the larynx, trachea, or esophagus, or as the result of distant metastases to vital areas.[5] Crile[3] reports 21 patients who have been followed for from five to twenty-one years or until their death. Only 3 have died from their disease, 1 with local recurrence in the thyroid and 2 from distant metastases. These 3 patients lived for nine, fifteen, and nineteen years respectively after the original thyroidectomy. One patient who has refused all treatment is living and well twenty-seven years after the appearance of lateral cervical nodules and twenty-one years after these nodules were proved to be papillary adenocarcinoma of the thyroid.

Histologically, the tumor is composed of small papillae of vascularized connective tissue projecting into the alveoli. The papillary projections may be covered with several layers of cuboidal or polyhedral epithelial cells varying considerably in size. Foci of solid masses of cells in which no lumen is discernible are encountered in the gland. Mitosis is moderately common and colloid may be present in relatively small amounts.

Fitzgerald and Foote[30] investigated the ability of such tumors to take up radioactive iodine. Twenty-nine patients with papillary adenocarcinomas were thus studied. Of this group, 21 failed to take up any radioactive iodine, while in 8 instances there was some concentration of the isotope either in the primary or metastatic lesions or both. In these 8 patients the tumor showed some histologic variations from the predominantly papillary form in that they demonstrated either follicle or alveolar formation or both. Rawson and his group[3] similarly found that the capacity of these tumors to take up radioactive iodine was minimal.

The *treatment* of papillary adenocarcinoma consists of the use of both surgery and postoperative irradiation. It is important to emphasize that with this type of tumor the presence of cervical lymph node metastases *is no contraindication for operation*. The operation must include the total removal of the thyroid lobe harboring the primary neoplasm and the removal of the involved cervical nodes. Subtotal lobectomy may result in a recurrence of the malignant tumor in the remnant of thyroid tissue.[6] Where the tumor is present in both lobes of the thyroid, total thyroidectomy would appear to be indicated unless the malignant focus in one lobe is so small as to permit the preservation of a small amount of thyroid tissue. There is a good deal of difference of opinion as to whether extensive cervical dissection should be resorted to in patients with papillary tumors with cervical node involvement. Limited dissection in which the visibly involved nodes in the neck and mediastinum are removed is recommended by some,[3, 6] while others suggest extensive cervical dissection with the

removal of lymphatic tissue from the clavicle to the mastoid process.[25,31,32] The results obtained with x-ray therapy alone are unsatisfactory,[2-4] but it has improved the prognosis when used postoperatively.[4] The recurrence of metastatic cervical nodes after operation calls for further surgical intervention with removal of the involved nodes.

The results obtained with use of radioactive iodine in the treatment of this tumor and its metastases are at present poor. Most thyroid papillary carcinomas fail to take up any radioactive iodine, while the few that do concentrate the isotope in only minimal amounts. If the capacity of the metastatic lesions of these tumors for the uptake of radioactive iodine can be increased by radiation or surgical thyroidectomy or by the use of thyrotropin or the thiouracils, this could be a valuable agent in the treatment of the papillary metastases.

Alveolar and Follicular Adenocarcinoma.—Pure alveolar or follicular carcinomas are rare and occurred in approximately 7 per cent of the patients with thyroid carcinoma reported by Frazell and Foote.[5] Some areas of alveolar or follicular structure, however, are seen in most thyroid tumors, but these areas constitute only a small part of the mass. The alveolar tumors usually occupy one lobe of the thyroid, are of moderate size, and as a rule are well encapsulated. Their histologic structure is orderly and resembles normal thyroid tissue or adenomas so closely as often to be regarded as benign until distant metastases occur. It is for this reason that they have been referred to as "benign metastasizing struma," a term which is a misnomer. The alveolar carcinomas involve the regional lymph nodes and may metastasize through the blood stream to the lungs and bones.

The alveolar and follicular carcinomas are distinctly more malignant than are the papillary adenocarcinomas but still fall into the group of relatively moderate malignancy. Patients may live for many years after the onset of the disease and even after the development of bone metastases. About 30 per cent of the patients reported by Frazell and Foote[5] were alive and well five years after the first visit to their clinic. This type of tumor occurs only slightly more frequently in females and in a somewhat older age group than is the case with the papillary carcinomas. However, the alveolar carcinomas also occur in very young people as well as in very old ones. A preexisting goiter is common.

The treatment of this type of tumor consists of the complete excision of the tumor tissue before distant metastases occur, followed by roentgen therapy. Where postoperative irradiation is used, Rawson[16] advises that it be given in doses of 4000 to 6000 roentgen. The alveolar and follicular carcinomas of all thyroid cancers are most likely to take up radioactive iodine. Of 39 such cases studied by Fitzgerald and Foote,[20] 29 (or 74 per cent) showed evidence of concentration of the radioactive isotope in the tumor tissue. The alveolar areas as a rule do not tend to concentrate the isotope, but the more differentiated the tumor and the more closely it resembles the normal thyroid follicular pattern the greater the likelihood of its concentrating radioactive iodine. According to Rawson and his group,[23] despite the fact that these tumors may contain recognizable fol-

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in the older age group and the median age of the series reported by Frazell and Foote[illegible] was sixty-one years. The tumors are large and bulky are highly infiltrative extend locally in the neck and often produce obstruction of the trachea and esophagus Histologically the tumor consists of anaplastic thyroid tissue growing in the form of giant cells

The clinical course is usually rapidly downhill and death generally results from obstructive manifestations rather than from metastases By the time these patients are seen the disease is usually inoperable and their response to x ray therapy is negligible Six patients studied by Fitzgerald and Foote[19] failed to concentrate any radioactive iodine.

The *small cell carcinoma* is an equally highly malignant tumor occurring as a rule in patients beyond the age of fifty years This tumor like the giant cell carcinoma is very invasive and unresponsive to the available forms of therapy

Epidermoid carcinoma of the thyroid is probably derived from remnants of the thyroglossal duct and is made up of squamous epithelium [15] This highly malignant tumor is fortunately rare but when it occurs it is invasive metastasizes extensively and is almost impossible to eradicate surgically [15]

Lymphosarcoma of the thyroid is a very rare disease Of 15 000 patients subjected to thyroid surgery at the Crile clinic between the years 1924 and 1945 only 8 instances of lymphosarcoma were encountered [36] This disease occurs predominantly in women and in the middle-aged group There is generally a history of recent rapid enlargement of the thyroid and only infrequently has a goiter been present for any considerable period of time Difficulty in breathing dysphagia and particularly unilateral vocal cord paralysis are quite common The tumor is highly malignant grows rapidly and is locally very invasive These tumors are usually not surgically curable and although they are very sensitive to irradiation good results are rarely obtained [36] Death usually occurs within a year after the onset of the disease

The pathologic picture of lymphosarcoma of the thyroid may be confused with small cell carcinoma and indeed most thyroid sarcomas probably are anaplastic carcinomas [3, 38] Occasionally lymphosarcoma may be confused with *struma lymphomatosa* The pathologic description of the cases reported by Dinsmore Dempsey and Hazard[36] is as follows The thyroid is extensively invaded in lymphosarcoma and the tumor is firm and tough in consistency The cut surface is usually pale gray yellowish gray or white in color with occasional brownish or purplish patches On microscopic examination it is seen that the neoplastic tissue tends to almost completely replace normal thyroid parenchyma The cells for the most part seem like small lymphocytes except for some irregularity of the dark-staining nuclei In addition there are areas of lymphoblasts and there are no reticulum fibers surrounding individual tumor cells or cell groups The neoplastic cells invade veins and venules muscle fat and fibrous tissue adjoining the thyroid sections *Struma lymphomatosa* is distinguished from sarcoma in that the lymphatic cell infiltration in the former is limited by bands of connective tissue separating the thyroid plates and lymph nodules are usually prominent and well formed In addition in *struma lymphomatosa* the typical cell is partly of the plasma cell type and oxy-

licular structures their functional capacity does not approach that of normal thyroid tissue.

Solid Adenocarcinomas.—The solid adenocarcinomas are the second most common form of thyroid cancer.[5] These tumors are more malignant than the alveolar carcinomas. They occur in approximately equal proportion in males and females, and the age incidence is somewhat similar to that of the alveolar carcinomas. Frazell and Foote[5] describe cases occurring in people varying in age from sixteen to seventy-six, the median age being forty-nine years. As with the other types of malignant tumors, a preexisting goiter was present in most instances.

The solid adenocarcinomas are large bulky tumors often involving more than one lobe. They are hard unencapsulated tumors with a tendency to infiltrate the surrounding tissue so that obstructive symptoms not uncommonly occur. Histologically they consist of clumps of cells without lumens and in general with little or no tendency to form follicular or papillary processes.[5] Local spread to regional lymph nodes and pulmonary and bone metastases occur.

The *treatment* consists of the complete surgical removal of the tumor tissue when possible followed by intensive x-ray treatment. According to Frazell and Foote,[5] however, irradiation does not particularly influence the course of this type of tumor. The ability of these tumors to take up radioactive iodine is dependent essentially on whether histologically they are predominantly solid or consist of ample alveolar, follicular, or papillary areas. In 8 cases of predominantly solid tumors only 1 was capable of concentrating the radioactive isotope while all 4 of the mixed variety showed positive radioautographs.[30] As with all types of thyroid neoplasms which take up radioactive iodine, there is a great variability in the concentration of the isotope in different areas in the same tumor.

Hurthle cell Carcinoma.—The Hurthle-cell adenocarcinoma is a tumor of moderate malignancy occurring mostly in middle age and predominantly in women. Frazell and Foote[5] report 1 instance in a patient twenty-one years of age, and 2 instances have been reported in infants.[33,34] These tumors constitute about 10 per cent of the thyroid carcinomas.[5] They are generally small, well encapsulated, and histologically are made up of cells containing abundant cytoplasm staining brightly pink with hematoxylin and eosin. The tumor may be made up of large polyhedral cells with the acidophilic cytoplasm and of small polygonal cells.[35] The latter cells may form alveoli or may be diffusely infiltrating. These tumors pursue a prolonged clinical course, grow slowly, and metastasize late. Although they generally tend to metastasize locally, distant spread to lungs and bone may occur. Of the 27 patients reported by Frazell and Foote,[5] a third were alive and free of the disease after a five-year follow up.

The *treatment* of the Hurthle-cell tumor, as of the other thyroid malignant neoplasms, consists of the complete surgical excision of all tumor tissue and the use of postoperative irradiation. Only infrequently do these tumors take up radioactive iodine and then only in the alveolar areas and only in minimal amounts.[30]

Giant Cell Tumors.—The giant cell carcinomas are very malignant tumors which constitute about 15 per cent of the thyroid carcinomas. They occur

factors Of 7 patients receiving thiouracil after thyroidectomy, in none did there occur an increase in the uptake of radioactive iodine [42]

The beneficial effects which follow surgical or irradiation thyroidectomy are theoretically dependent on two factors By eliminating normal thyroid tissue an important source of competition for available radioactive iodine is thus removed And secondly the increased production of thyroid stimulating hormone which follows the removal or destruction of the thyroid increases the functional capacity of metastatic thyroid tissue to concentrate radioactive iodine Thus similarly the injection of thyroid stimulating hormone or the *oral ingestion of the thiourea compounds induces* hyperplasia of thyroid tissue increasing its ability to take up the isotope



FIG 84 —Colloid goiter Note excessive colloid storage with flattening of the cuboidal acinar cells and decrease of the interstitial cells (Courtesy Dr W D Collier)

The treatment of carcinomatous thyroid metastases with radioactive iodine includes the following measures Tracer studies with radioactive iodine are conducted to determine whether the metastatic areas take up ample amounts of isotope In the event that the uptake is minimal the patient is subjected to one or more of the procedures described above in an effort to increase the concentration The patient is then given I_{131} orally *The total dosage generally required for destruction of the metastatic lesions* may vary from as little as 100 to as much as 1000 millicuries Approximately 100 millicuries are administered every six to eight weeks until such time as the metastatic tissue no longer takes up any of the radioactive isotope

Hazards of Treatment with Radioactive Iodine —The use of radioactive iodine in the larger doses necessary for the treatment of carcinomatous metastases is sometimes followed by certain toxic manifestations which may be serious Trunnell and his coworkers[44] observed some degree of

phatic follicles are distributed through the infiltrate. Finally, infiltration of structures adjoining the thyroid gland does not occur.

The Use of Radioactive Iodine in the Treatment of Metastases from Carcinoma of the Thyroid.—In 1942 Keston and his coworkers[39] reported the selective concentration of radioactive iodine in a metastatic lesion secondary to thyroid carcinoma. This was the first time that concentration of the isotope was demonstrated in thyroid tumor tissue, but no definite treatment was undertaken. In 1946, Seidlin, Marinelli and Oshry[40] reported the first case of carcinoma of the thyroid with metastases that was treated with radioactive iodine. The metastatic lesions collected the isotope and a considerable degree of clinical improvement followed. It promptly became evident that most metastatic lesions unfortunately failed to concentrate radioactive iodine. Thus, of 25 patients with carcinoma of the thyroid with metastases reported by Trunnell and his coworkers[41] only 1 had metastatic tumor tissue which could take up enough radioactive iodine to justify some enthusiasm for its therapeutic use. At the Mount Sinai Hospital of 71 patients studied by Yohalem, Feitelberg and their group[4], 16 could concentrate the isotope either in the metastases or in the thyroid carcinoma. By far and large this is the general experience unless specific methods are employed to stimulate the metastatic tissue to greater functional capacity for the radioactive isotope.

Seidlin and his coworkers[42] and independently but somewhat later Rawson and his group[44] demonstrated that the complete surgical removal of the thyroid gland or its destruction with *x*-ray or radioactive iodine resulted in an increase in the uptake of the isotope by previously poorly functioning metastatic cancer. In addition, metastatic tissue which prior to treatment could take up *no* radioactive iodine was now capable of concentrating the isotope. The surgical removal of the thyroid gland or its destruction was carried out in 23 patients with carcinoma of the thyroid with metastases by Trunnell and his group.[41] One or more metastases in 12 of these patients were subsequently observed to concentrate more radioactive iodine than before removal of the gland. Of 10 patients similarly treated, Yohalem, Feitelberg and their coworkers[4] found that 2 could now take up the radioactive isotope where none could be collected before.

This method therefore represents an important advance in the treatment of thyroid carcinoma with metastases with radioactive iodine. Seidlin and his group[45] regard thyroidectomy as a basic step in the treatment of this disease. This may be accomplished either by the surgical removal of the gland or by the use of *x*-ray therapy or with radioactive iodine (I_{131}). Attempts were made to further increase the uptake of radioactive iodine by treatment with thyroid stimulating hormone of the adenohypophysis[41,42] and by the use of goitrogenic agents such as thiouracil and propylthiouracil.[41] The injection of 30 mgm. a day of the thyroid stimulating hormone (T.S.H.) for five or more days to several totally thyroidectomized patients and to one before thyroidectomy resulted in a considerable increase in the avidity of the metastatic lesions for radioactive iodine.[41,42] Similarly, in 7 of 10 thyroidectomized patients there occurred an increase in the uptake of the isotope following the prolonged use of thiouracil or propylthiouracil.[41] Our results with the latter agents have been less satis

former, 10 to 27 per 1000 of population have enlarged palpable thyroids of varying degrees in contrast to less than 1 per 1000 of population in the eastern states There is, of course a good deal of difference in the incidence of endemic goiter in the various endemic areas and even in different communities within the same area In general however, goiter is considerably more common in the goitrous regions of the Alps and Himalayas than in the most goitrous belt in the United States or England

Greenwald[47] denies the existence of any relationship between endemic goiter and iodine lack In a detailed study and analysis of available date previously reported by various investigators he has emphasized these several points 1 There is no decrease in the absolute iodine content of the goitrous thyroid glands Indeed the larger glands according to Greenwald, tend to contain more iodine 2 Although goiters have been produced in rats on certain iodine-poor diets the addition of small quantities of iodine comparable to that found in ordinary diets will not prevent nor lessen the thyroid enlargement The administration of large quantities of iodine however will result in glands of normal microscopic appearance and size 3 The prophylactic administration of iodine to humans has not reduced the incidence of new goiter to zero and in some cases has had no effect or even increased the frequency 4 Persons with goiter in this country do not show the usual signs of thyroid insufficiency 5 The evidence that there is a deficiency in the iodine intake in goitrous regions is faulty in that neither the analytic technics nor the collection of food water and excreta were well controlled

Most careful investigators however and the extensive studies available favor the role of iodine lack in the pathogenesis of endemic goiter, although other factors unquestionably are of importance The factors most commonly considered are infection, pollution of water supply [52] and the presence of goitrogens in food and medicines The goitrogens are of course capable of producing enlargement of the thyroid gland and such agents are present in many vegetables Chesney Clawson and Webster[53] demonstrated the goitrogenic action of cabbage and it was subsequently shown that goitrogenic properties of cabbage are seasonable being present in fall and winter cabbage and absent in the spring and summer variety [54 55 56] Similar goitrogenic properties are attributed to related vegetables such as Brussels sprouts and cauliflower Kennedy and Purves[57] have demonstrated goitrogenic properties in rape seed and Sharpless Pearsons and Prato[58] showed that soy beans are occasionally goitrogenic Finally certain medicaments such as potassium thiocyanate [59] and now the thiourea derivatives are capable of producing thyroid enlargement

Since the various goitrogenic agents are present in foods which are common articles of diet it is conceivable that in communities where such food is eaten in abundance goiter may result in the presence of a normal iodine content of both food and water

Sporadic goiter is 5 or 6 times as common in females as in males The ratio of females to males in endemic goiter becomes progressively less as the concentration of goiter in a particular region becomes greater This is due not to the less frequent involvement of females in these areas but to the increasing number of males who are afflicted as more and more members

depression of hematopoiesis in all their patients treated intensively. The earliest change usually encountered is a decrease in the absolute number of circulating lymphocytes. Later, there may occur a thrombopenia and a reduction in hemoglobin and the red blood cell count. Bone marrow aspirations have been reported to show a decrease in the total cell count, a relative increase in erythroid activity, and a decrease in myeloid elements.[41]

Amenorrhea with hot flashes is occasionally induced by the administration of large doses of radioactive iodine. This complication occurred in 3 of Trunnell's patients.[41] In 2 of these patients the urinary gonadotropin excretion remained within the normal range. This would suggest that the amenorrhea was the result of the direct effect of the radiation on the ovary rather than on the adenohypophysis. Three patients developed clinical signs and symptoms of hyperthyroidism within two weeks after the radioactive iodine was administered. In all 3 the diagnosis was further confirmed by an elevation of the serum protein bound iodine.[41] The authors attribute this complication to the destruction of thyroid tissue with release of thyroglobulin.

Endemic and Sporadic Colloid Goiter

By endemic goiter we refer to the enlargement of the thyroid gland commonly found among the inhabitants of certain specific regions of the globe. Sporadic goiter has reference to a histologically and clinically similar condition but occurring in isolated individuals anywhere. The term colloid goiter is really a pathologic description and refers only to one aspect in the pathologic development of the disease. The colloid goiter common during the adolescent period of life, particularly in females, is a similar process although of a much milder degree. This occurs when the physiologic demands are greater than the thyroid gland can cope with under *given environmental iodine conditions*. Long ago Marine emphasized that iodine want induces thyroid hyperplasia and that the administration of iodine to such individuals will result in involution of the hyperplastic gland.

During the course of the past century a good deal of evidence has accumulated to indicate the close relationship which exists between endemic goiter and the iodine lack in those areas. The regions of endemic goiter include the Himalayan plateau of Asia, the Alps, Pyrenees, and the Carpathian mountain regions of Europe, the Andean plateau of South America, and the St. Lawrence, Great Lakes, and Rocky Mountain regions of North America. In these areas where goiter is so common the soil, water, and vegetation are relatively poor in iodine.[46] Goiter was apparently not present in England prior to the eighteenth century,[47] but the southwest corner has since become goitrous.[48] The most goitrous parts of the United States are the northwestern block of states together with Michigan, Wisconsin, and Colorado. The least goitrous include New England, New Jersey, Maryland, and the southern states from the Atlantic Coast along the Gulf, including Texas and New Mexico.[49] According to Olesen,[50,51] the over-all incidence of goiter in the endemic regions of the United States may be 10 to 30 times as great as that in the non-goitrous areas. In the

The prevention of goiter according to Kimball[60] is best carried out by the use of iodized salt and he recommends a concentration of 0 01 per cent or 1 part of sodium iodide to 10 000 parts of salt Actually the iodized salt in this country is so standardized that twice this recommended amount of iodine is present the concentration of sodium iodide being 0 02 and that of potassium iodide 0 023 per cent This will yield a daily iodine intake to the average salt consumer of slightly more than 1 mg a day Such amounts are considerably in excess of the daily iodine requirement According to Eggenberger[61] the daily iodine requirement is somewhere between 1 and 2 gamma per kilogram of body weight roughly 0 075 to 0 15 mg The question of whether the administration of excessive amounts of iodine to individuals with iodine deficient goiters is capable of producing thyrotoxicosis or Jod basedow is discussed in some detail elsewhere p 827 In any event this complication apparently so common on the continent, is rare here

Marine[62] and later Kimball,[60] summarized this general problem of endemic goiter by emphasizing the following facts

1 Endemic goiter is a deficiency disease due to the lack of iodine in food and drink 2 The addition of an exceedingly small amount of iodine to food in endemic goiter regions prevents goiter The most practical method available is the use of iodized salt 3 By preventing endemic goiter the incidence of adenomas toxic goiter cretinism deaf mutism idiocy and various congenital abnormalities will be considerably reduced

Amyloidosis of the Thyroid Gland (Amyloid Goiter)

In 1942 Walker[63] collected 56 cases of amyloid goiter from the literature and added 2 of his own He found that amyloid goiter was almost invariably associated with generalized amyloidosis and most frequently secondary to a chronic disease Amyloid of the thyroid alone was reported in only 2 instances Pathologic studies reveal that the amyloid is associated with a striking infiltration of the gland with fatty tissue The gland becomes enlarged and firm and at times may be clinically confused with carcinoma Although the amyloid infiltration may be marked thyroid insufficiency as a rule does not occur More recently Means[49 64] has encountered 2 cases, one of which we have had the opportunity to study

Illustrative Case of Amyloid Goiter

A twenty-seven year old man was admitted to the Mount Sinai Hospital in 1947 with a thirteen year history of recurrent episodes of rheumatoid arthritis For six months prior to admission he had noted a swelling over the lower anterior region of the neck He had been hospitalized elsewhere where a diagnosis of amyloid disease of the thyroid was established

The physical examination revealed a chronically ill appearing man with a slight lid lag of the right eye The sublingual and submandibular glands were increased in size The thyroid was markedly and diffusely enlarged firm and smooth There was no thrill palpable nor any bruit audible over the gland The spleen was readily felt but the liver was not palpable There were spindle shaped swellings of the phalangeal joints and atrophy of the muscles of the shoulder girdle and hands In addition there was limitation of motion of the

of the community develop the disease. The peak of incidence occurs at an earlier age in boys than in girls. In general, the peak for boys is reached between the ages of eleven and fourteen and for girls between fourteen and seventeen.[49]

The clinical picture of endemic goiter is dependent essentially on the severity and age of the endemic areas. Certain regions in Switzerland for example have been severely goiterous for many generations with continuous inbreeding of the population. The clinical picture encountered in such areas differs in degree from that observed in any of the goitrous regions in this country. In the milder endemic regions, a swelling at the base of the neck becomes evident in some portion of the population long before puberty and as the age of puberty approaches more and more members of the population are afflicted and the goiters become progressively larger. After puberty the colloid goiters in boys may become smaller and even disappear. In girls the goiter may increase in size to the age of seventeen or eighteen and may either increase or decrease in size thereafter but few if any will disappear.[49] The basal metabolic rate may be slightly reduced but otherwise there are no significant clinical manifestations. The gland which is generally soft and free from thrills or bruits will increase somewhat in size during pregnancy but will otherwise exercise no effect on gestation. The offspring in the mild endemic areas such as exist in the United States at present is non-cretinous. In the severe endemic areas the children are involved at an earlier age, the goiters are much larger, and the incidence of endemic cretins and adults with severe hypothyroidism becomes progressively greater. Endemic congenital cretins are the result of several generations of endemic goiter.

The goiters are generally soft and smooth early in life but as the individuals grow older and approach middle age the gland becomes irregular, lumpy and nodular. The irregularity may be due to localized areas of involution with the formation of colloid nodules which are often encapsulated. Cysts containing sometimes a clear and rather thin fluid and at others evidence of recent or old hemorrhage may be present and produce nodular irregularities. As described elsewhere in this book these nodular goiters may become hyperplastic with the development of clinical hyperthyroidism and finally malignant neoplastic changes may take place.

Treatment of Endemic and Sporadic Goiter. — *The treatment of the individual with goiter* consists of the administration of iodine and of small amounts of thyroid extract. The former may be given in amounts of 1 to 3 mgm. of potassium iodide per week and the latter in a dosage of 0.5 to 1.5 grains of thyroid extract daily. During the early stages of goiter when the gland is still hyperplastic the administration of iodine may result in considerable improvement. With the development of the hyperinvolutionary or colloid stage iodine exercises relatively little effect.[49] Thyroid extract particularly in the presence of a low basal metabolic rate may induce a decrease in the size of the gland. Both agents should particularly be administered to pregnant women with goiter. Surgical removal of the goiter is indicated when the gland is unduly enlarged, when it produces pressure symptoms or when it suddenly increases in size.

The prevention of goiter, according to Kimball[60] is best carried out by the use of iodized salt and he recommends a concentration of 0 01 per cent or 1 part of sodium iodide to 10 000 parts of salt Actually the iodized salt in this country is so standardized that twice this recommended amount of iodine is present the concentration of sodium iodide being 0 02 and that of potassium iodide 0 023 per cent This will yield a daily iodine intake *to the average salt consumer of slightly* more than 1 mg a day Such amounts are considerably in excess of the daily iodine requirement According to Eggenberger[61] the daily iodine requirement is somewhere between *1 and 2 gamma per kilogram of body weight roughly 0 075 to 0 15* mg The question of whether the administration of excessive amounts of iodine to individuals with iodine deficient goiters is capable of producing thyrotoxicosis or Jod basedow is discussed in some detail elsewhere p 827 In any event this complication apparently so common on the continent is rare here

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right knee and hip The urinalysis revealed a considerable albuminuria with occasional hyaline and granular casts and 8 to 10 red blood cells per high power field The specific gravity of the urine was fixed at 1010 The blood hemoglobin was 12 grams per cent, and the red blood cell count was 4 16 million per cubic millimeter The sedimentation rate (Westergren) was accelerated being 123 mm per hour The blood urea nitrogen was 16 mgm per cent The basal metabolic rate was −17 per cent The congo red test demonstrated 100 per cent retention

Three months following his discharge from the hospital he was again admitted because of nervousness insomnia, a weight loss of 15 pounds and cardiac palpitation

The physical examination at this time revealed a marked stare in addition to the findings previously observed The heart rate was rapid and a fine tremor of the outstretched hand was apparent The hemoglobin was now 8 grams per cent, and the red blood cell count was 3 0 million per cubic millimeter The circulation time (arm to-tongue) was seven seconds The blood urea nitrogen was increased to 50 mgm per cent The basal metabolic rate ranged from +46 to +62 per cent The twenty four hour urinary excretion of a tracer dose of I_{131} was only 2 per cent The serum protein bound iodine was 24 micrograms per cent

The diagnosis of hyperthyroidism was established and he was treated with a therapeutic dose of 11 25 millicuries of I_{131} followed by the administration of Lugol s solution When the basal metabolic rate had returned to normal levels he was subjected to subtotal thyroidectomy because of the tremendous size of the gland The pathologic report of the specimen was as follows ' Thyroid showing diffuse amyloid infiltration with glandular parenchyma showing evidence of recent and preceding hyperplasia Amyloid in vessels and in basement membrane of the sebaceous glands of the skin Postoperatively, the basal metabolic rate fell to −1 per cent He was discharged for further observation

Thyroglossal Duct Cysts —Thyroglossal cysts may result from the persistence of the thyroglossal duct The first manifestations of such a disorder are usually observed in infancy or childhood although rarely they first become apparent in adult life The cyst is located in the midline anywhere along the part of the normal embryologic course of thyroid migration It may drain internally through an opening at the foramen cecum but external drainage occurs only if the cyst becomes infected and ruptures or is incised surgically When this occurs intermittent drainage from a permanent sinus results The external sinus opening usually is located between the hyoid bone and the thyroid isthmus and the sinus tract may be palpated as a cord from the external opening to the level of the hyoid Other cystic structures such as branchial cysts must be differentiated from thyroglossal duct cysts The former do not occupy a midline position

The treatment of a thyroglossal cyst consists of the surgical excision of the entire sinus tract and cyst Inadequate removal will invariably be followed by recurrence

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thymus the thymocytes disappear rather abruptly as one proceeds from cortex to medulla The medulla consists principally of reticular cells the lymphocytes being much fewer in number In addition in the medulla there are rounded acidophilic structures varying from 30 to 100 micra in diameter which are called Hassall s bodies They consist of concentrically arranged cells, the outermost of which are connected with the reticular cells In the centers of these bodies evidences of degeneration and hyalinization and even small cysts may be observed At times calcium may be deposited in these areas This inner medullary region is more vascular than the cortex and some connective tissue cells are seen around the vessels Occasionally myelocytes and plasma cells may be seen but germinal follicles are rare The reticular cells are epithelial in origin, being derived from an entodermal anlage These cells are often difficult to distinguish histologically from connective tissue cells However, if the lymphocytes are destroyed by *x* ray their structure becomes more evident Further proof of their epithelial origin is afforded by tissue culture studies The thymic reticular cells differ from reticular cells elsewhere in that they do not collect intravital dyes, although under certain circumstances they may store iron and lipoid and may contain dead lymphocytes Reticular fibers are relatively scarce being located chiefly about the blood vessels where there are also some mesodermal reticular cells

The identity of lymphocytes and thymocytes is accepted by most investigators This is based not only on their morphologic similarities but also on the equal susceptibility of both to *x* ray to cytolysis by sera obtained by the injection of thymus cells into rats and the ability of both to transform into macrophages The mitochondria are similar in both types of cells In tissue culture it can be demonstrated that the small round cells are not derived from the reticular cells The fact that the thymocytes can be transformed into plasma cells and eosinophilic myelocytes would seem to prove the hematic and mesenchymal origin of these cells

The *arterial* supply of the thymus is derived from the internal mammary and the superior and inferior thyroid vessels These arteries are first distributed to the cortex Return drainage of blood from the thymus is effected by large vessels which arise in the medulla and empty into the thyroid and left innominate veins The lymphatics course chiefly in the interlobular connective tissue and drain into the anterior mediastinal sternal and tracheo bronchial lymph nodes The nerve supply which is probably chiefly of a vasomotor nature is derived from the vagus and the sympathetic nervous system These branches which are derived from the *descendens hypoglossi* and *phrenic* nerves reach the capsule but do not penetrate into the substance of the gland

The thymus begins its development during the sixth week of fetal life (10 mm) as a pair of solid buds from the ventro lateral walls of the third pharyngeal pouches and fuse during the third month At times the fourth pouches also give way to some thymic tissue The lumen of the proliferating bud soon disappears and the epithelial sprouts invade the sur ding mesenchyme The lobules arise from the branching of these l al strands The thymocytes are derived from the inwandering of id cells which originate in part from the perivascular mesenchymal

cells With the growth of the gland, the lymphocytic cells continue to enter the organ and to proliferate within the thymus The epithelium is converted into a reticular mesh filled with lymphoid cells and penetrated by blood vessels The medulla arises by a proliferation of the epithelial mass in the deeper portion of the lobules At the same time the lymphocytes in these areas degenerate or migrate Later Hassall s bodies are derived from the reticular cells by processes which as yet have not been completely clarified

The *physiologic* functions of the thymus are unknown The thymus, as has been mentioned increases in size to the age of puberty and then regresses The cortex begins to involute at about the age of two to four years the medulla at puberty During the earliest phases of involution the lymphoid cells in the cortex begin to thin out and adipose tissue begins to replace the compressed reticular cells In the medulla the last elements to be replaced are the Hassall s bodies Although involution is a physiologic phenomenon it may be hastened or delayed by several factors The administration of adrenocorticotropin or various adrenal corticoids to the intact rat will produce a marked reduction in the size and weight of the gland Estrogens and to a lesser degree androgens whether administered exogenously or as the result of stimulation of the gonads by gonadotropin will also result in atrophy of the thymus These observations probably account for the reduction in size of the thymus that begins at puberty In contrast castration will prevent this involution The adrenal mechanism explains a wide variety of factors that cause shrinkage of the thymus Starvation toxins morphine *etc* are all types of stress that provoke the liberation of adrenocorticotropin and of the adrenal cortical steroids It thus becomes apparent that hypophysectomy or adrenalectomy will prevent the decrease in thymic size that follows stress In such animal preparations the thymus is usually large If in addition, gonadectomy has been performed the thymus will be found to be maximum in size Growth hormone has a direct stimulating effect on thymic size even in the hypophysectomized animal On the other hand, a pyridoxine deficient diet and such agents as nitrogen mustards or sodium cacodylate cause a direct toxic destruction of the thymus

Removal of the thymus is apparently without observable effect in the experimental animal No definite evidence is available that there is any thymic hormone although it seems likely that the breakdown products of the thymus resulting from adrenocortical secretion may play some physiologic role Rowntree and his associates[2] reported that the administration of thymic extracts to successive generations of rats resulted in marked acceleration of somatic growth and precocious sexual development in each succeeding generation However this work has failed of confirmation

It has been claimed that the thymus may play a role in calcium metabolism and in regulation of skeletal growth, since thymectomy may be followed by defective mineralization of bone as well as dwarfism [14] Gudernatch[17] reported that the feeding of thymus tissue to tadpoles stimulated their growth but inhibited metamorphosis In pullets and chickens following thymectomy eggs are reported to be laid with uncalcified shells [18]

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an incidence of only 10 to 15 per cent Thymomas in association with myasthenia gravis are more common in the age group between thirty and sixty and in males Castleman and Norris[5] believe that the thymomas associated with myasthenia gravis are benign in over 90 per cent In the remaining 10 per cent although local spread or implantation may occur, the histology is that of a benign growth The tumors are almost invariably encapsulated and may consist chiefly of epithelial or lymphoid elements or a mixture of both Hassall s corpuscles are rarely observed in these tumors

The histology of the thymus in most patients with myasthenia gravis unassociated with tumor is characterized by the presence of large numbers of germinal centers in the medulla It has been suggested that in the absence of tumor the thymus is frequently hyperplastic More recent pathologic studies however indicate that in most of the instances the thymus is perhaps no larger than is normally encountered at the various age groups[5] Nevertheless the surgical removal of non neoplastic thymic tissue was followed by improvement in the symptoms of myasthenia gravis in one-half the patients[5]

Our group[10] recently reported shrinkage of a thymic tumor following the parenteral administration of ACTH This was associated with considerable improvement in the symptoms of myasthenia gravis The symptoms recurred and the thymic mass returned to its original size sometime after cessation of therapy Torda and Wolff[18] have reported improvement in patients with myasthenia gravis without tumor following treatment with ACTH

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Asher and his associates have claimed that thymic extracts contain a growth promoting principle that stimulates the sex organs. However, these claims as well as those of Bomskov on the effects of the thymus on carbohydrate metabolism have not been confirmed.[15, 17]

It is apparent from this discussion that there are, at present, no demonstrable endocrine disorders of the thymus. This gland, however, is affected in certain of the diseases of the other endocrine glands and by some of the adaptative mechanisms of the organism. Infections, trauma and other stresses will result in a decrease in size of the thymus secondary to the elaboration of adrenocortical fractions. This was demonstrated by Selye[11] and by White and Dougherty[12] in the experimental animal and by Soffer, Gabrilove and their coworkers in man.[10] The latter investigators induced marked reduction in the size of a thymic tumor in a patient, with myasthenia gravis following the administering of adrenocorticotropin. In adrenal insufficiency and in hyperthyroidism, the thymus is frequently enlarged. Thymic enlargement is also encountered in acromegaly, hypogonadism and myasthenia gravis. Ordinarily this hyperplasia or persistence of a non involuted thymus is asymptomatic but may occasionally produce signs of tracheal compression.

The concept of *status thymo-lymphaticus* has been the subject of a good deal of controversy.[16] The sudden deaths attributed to this condition are associated at postmortem examination with an enlarged thymus, lymphoid hyperplasia, hypoplasia of the aorta, decrease in the size of the adrenal glands and underdevelopment of the gonads. The report of Turnbull and Young[16] is interesting in relationship to these findings in that similar pathologic observations were encountered in individuals dying suddenly of trauma at any age. The conclusions arrived at by the Commission investigating this problem[16] was to the effect that the enlarged thymus played no specific role in sudden deaths.

Apart from the specific adaptative and physiologic involution of the thymus, aplasia or hypoplasia is rare. Inflammatory disease of the thymus is uncommon but may occur in the course of sepsis. *Dubois abscess* is in reality a cyst of the thymus due to persistent embryonic duct.

Tumors of the thymus are uncommon. The usual types are *lymphosarcoma* derived from the lymphoid elements, *benign thymoma* and *thymic carcinoma*. Actually, it is questionable as to whether most instances of so called lymphosarcoma of the thymus are really lymphatic in origin. Many are probably instances of anaplastic carcinoma. Other less important tumors include *dermoid cysts, spindle cell sarcoma, lipoma, myxoma, fibroma* and *leukosarcoma*.

The important symptoms of thymic tumors are chiefly those due to pressure on adjacent structures such as tracheal compression and venous obstruction. As mentioned elsewhere in this text, instances of Cushing's syndrome have been reported in the presence of primary thymic carcinomas associated with bilateral adrenal cortical hyperplasia.

Myasthenia gravis is frequently associated with thymic hyperplasia or tumor.[4, 8] Castleman and Norris[5] have recently reviewed this problem and found thymomas present in almost 25 per cent of 330 cases of myasthenia gravis collected from the literature. Other observers have found

Chapter 29

ANATOMY, PHYSIOLOGY AND DISEASES OF THE PARATHYROIDS

HYPOPARATHYROIDISM, PRIMARY HYPERPARATHYROIDISM (VON RECKLINGHAUSEN'S DISEASE OF BONE), SECONDARY HYPERPARATHYROIDISM

The Gross Anatomy and Embryology of the Parathyroid Glands.—The parathyroid glands are small, yellowish brown, oval bodies that are found in intimate contact with the inner posterior surface of the lateral lobes of the thyroid gland. Each one is enclosed within its own connective tissue sheath and lies within the capsule rather than in the substance of the thyroid. Four parathyroid glands are usually present as Gilmour[1] observed in almost 90 per cent of 428 human dissections. He did find, however, that the number may vary from 2 to 6. Each parathyroid body is approximately 6 to 8 mm. in length, 3 to 4 mm. in width, and 1 to 2 mm. in thickness. According to Pappenheimer and Wilens[2] the total average weight of these glands may vary from 67 to 200 mgm., but greater total weights have been encountered in normal individuals.

The parathyroids are divided into superior and inferior groups, each consisting of 2 glands. The former are ordinarily encountered at the level of the lower border of the cricoid cartilage behind the junction of the pharynx and esophagus. The inferior set is usually found near the lower edges of the lateral lobes of the thyroid, or in relation to the inferior thyroid veins. Embryologically these structures are derived from outpocketings of the third and fourth branchial pouches on each side. They then migrate with the thyroidal anlage. The derivatives of the third pouch travel farther caudad than do those of the fourth, and as a consequence form the inferior parathyroids. During fetal life these latter structures are often in close relationship to the thymus, and as a result may at times be found within the thymus or in the mediastinal thoracic cavity. It is for this reason that no exploratory procedure for a parathyroid tumor is complete unless the superior mediastinum is carefully searched.

The blood supply of the parathyroid glands is derived from branches of the superior and inferior thyroid arteries. The main vessel supplying each gland enters at the hilus and then forms branches that course along the connective tissue septa. These arteries then empty into the sinusoidal vessels found in intimate contact with the cords of the epithelium. These capillaries are without a basement membrane but are surrounded by reticular fibers that separate them from the epithelium. The parathyroid vein leaves the gland at the hilus and empties into the nearby veins draining the thyroid and adjacent neck structures.

The nerve supply is derived from the cervical sympathetic and consists of unmyelinated fibers of the vasomotor type.

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of the serum varies from 9 to 11 mgm per cent Only negligible amounts are found in the red blood corpuscles In the serum calcium exists essentially in two forms Approximately 45 per cent of the total serum calcium is *bound to protein in the ratio of 0 84 mgm of calcium per gram of protein*[4] This moiety is nondiffusible and nonionized The remainder of the serum calcium is diffusible and almost entirely ionized A small portion of the diffusible fraction is perhaps bound in some sort of citrate like complex and is consequently nonionized McLean and Hastings[5,6] have devised a nomogram which enables one to calculate directly the level of ionized calcium if the total serum calcium and the total serum protein are known based on the formula

$$\frac{(Ca^{++})\ (Prot^{=})}{(Ca\ Prot)} = 10^{-2.22} \quad \text{at } T = 25\ C$$
$$pH = 7\ 35$$

Calcium is found in other body fluids such as the lymph aqueous humor ascitic and edema fluids and the cerbro spinal fluid in lower concentrations than is present in the serum The calcium content of the cerebrospinal fluid which is almost protein free is roughly equal to that of the diffusible *fraction of serum However the concentration of calcium in this compartment* is not affected by alterations in the plasma diffusible calcium concentration induced by the injection of calcium salts nor is it altered following parathyroidectomy

The evidence would seem to indicate that the parathyroid hormone influences the diffusible rather than the non-diffusible calcium fraction[4] and that it is this former fraction which is physiologically active[7,8] When the serum calcium level falls its urinary excretion decreases and ceases almost entirely when the serum level is below 7 mgm per cent[9]

The body contains phosphorus in both organic and inorganic forms The former fraction includes ester lipid and nucleic acid phosphorus The blood contains considerably greater amounts of organic than inorganic phosphorus the former being found for the most part in the cells The inorganic fraction ordinarily varies from 3 to 4 mgm per cent and is distributed equally between the cells and plasma It is with this latter fraction that we are particularly concerned

In general phosphorus is absorbed from the small intestine in an inorganic form *Its absorption and consequent availability is favored by* a low calcium intake a high vitamin D intake and an increase in the acidity of the intestinal content Normally it is excreted chiefly in the urine and somewhat less in the stool The renal threshold for the serum phosphorus is 2 to 3 mgm per cent

The serum phosphorus may fall temporarily following the ingestion of carbohydrate or the administration of insulin since this ion plays an important role in the intermediary metabolism of carbohydrate A reciprocal relationship exists between the concentration of the serum inorganic phosphorus and the serum calcium expressed by the formula $(Ca^{++})\ (PO_4^{=}) = K$ Although at times both may be reduced as in rickets normally in adults the product of the concentrations of serum calcium and serum inorganic

The Histology of the Parathyroid Glands —Histologically the parathyroid glands consist of densely packed epithelial masses strands and cords of cells throughout which course sinusoidal capillaries separated from the epithelium only by reticular fibers There are two main types of cells the *principal* or *chief* cells and the *oxyphil* or *eosinophilic* cells The chief cells which are said to be the only cells in the parathyroids up to the age of ten years are pale and clear and granules are but rarely noted in the cytoplasm They vary in size from 6 to 8 microns in diameter and contain a nucleus which is large and vesicular At times these cells are arranged in follicles in the lumen of which some colloid like material is found This colloid substance consists of a homogenous protein material which lacks iodine Parathyroid colloid when it is present generally appears after puberty The eosinophil or oxyphil cells are larger than the clear cells being 11 to 14 microns in diameter and the granular cytoplasm stains deeply with acid dyes The nuclei are small and dense Both dark and light oxyphil cells have been described It is generally believed that the oxyphil cells are physiologically inert although parathyroid adenomata consisting of eosinophil cells have been reported in hyperparathyroidism These cases however are not accepted by Castleman and Mallory [3] Mitochondria and Golgi apparatus are present in both types of cells and in addition the chief cells usually contain glycogen and neutral fat Large vacuolated water-clear cells have also been described When small these cells resemble chief cells and for this reason Castleman and Mallory [3] have suggested that they represent transitional cells to indicate their derivation from the chief cells These investigators [3] have proposed a monophyletic theory of origin of all the cells of the parathyroid the chief cell being the parent cell from which both the water clear cell and the oxyphil cell are derived

The Physiology of the Parathyroid Glands —The physiologic actions of the parathyroid hormone are intimately concerned with the metabolism of calcium phosphorus and bone Calcium is normally ingested in the food and excreted through the urine and stool Under normal circumstances the fecal loss exceeds that in the urine This is in contrast to the far greater urinary excretion of calcium which is encountered in hyperparathyroidism Since calcium is constantly being excreted by the organism if the intake is greatly restricted a negative balance ensues The daily adult requirement is approximately 1 gram The availability of the ingested calcium depends on its absorption from the upper small intestine Absorption of this electrolyte is favored by an increased acidity of the intestinal contents a high vitamin D intake a relatively low phosphorus content of the food and adequate digestion and absorption of fat In general any agents or factors that will result in the precipitation of insoluble calcium salts such as the presence of oxalates or phytic acid in the food will decrease the absorption and therefore the availability of this ion Under circumstances where the loss of calcium is excessive such as occurs for example during lactation a positive balance can only be obtained by greatly increasing the amount of calcium ingested

Approximately 2 per cent of the body weight consists of calcium almost all of which is found in the skeletal system The normal calcium content

is readily precipitated Other mechanisms perhaps involving local alterations of pH may help explain the deposition of the carbonate salts

The serum alkaline phosphatase is derived for the major part from bone where it is secreted in large quantities by the osteoblasts at the sites of active bone formation In the absence of hepato-biliary disease the serum alkaline phosphatase may serve as an index of bone formation

Whether the osteoclasts actively destroy bone or act as phagocytes in cleaning up bone debris is still unknown However wherever and whenever bone destruction is proceeding these cells are found in great number Whether they are derived from osteocytes or represent foreign body giant cells or a specific type of cell is obscure

The Metabolic Effects of Parathyroid Hormone —When parathyroid hormone is administered to the experimental animal or to the human it is followed by an increase in the urinary excretion of phosphorus a decrease in level of the serum inorganic phosphorus an increase in the serum calcium level and an augmented urinary calcium excretion [17] In addition its prolonged use results in bony changes characterized primarily by osteoporosis and by osteitis fibrosa The biochemical antithesis of this is observed following the removal of the parathyroids There occurs a decrease in the urinary excretion of phosphorus an increase in the serum level of inorganic phosphorus associated with a fall in the serum calcium and a decrease in the urinary excretion of calcium Parathyroid hormone exercises no effect on the gastrointestinal absorption of calcium or its fecal excretion The two most widely accepted hypotheses proposed to explain these phenomena are that the parathyroid hormone primarily regulates the renal excretion of phosphate ion[14] or that it directly acts to withdraw bone salts from the bone [18,19,20] The arguments marshalled in favor of each of these theories have included facts which ostensibly directly support the proposed hypothesis as well as evidence incompatible with the opposing view Albright and his associates [1] have demonstrated that the increase in the urinary excretion of phosphorus is the first effect noted following the administration of parathyroid hormone In addition the urinary phosphate loss in comparison to the urinary calcium loss is greater than that observed when decalcification of bone is experimentally induced by the administration of acidifying salts such as ammonium chloride [21] Although some observers have been unable to confirm their results Harrison and Harrison[22] demonstrated that the administration of parathyroid hormone resulted in a decrease in the renal tubular reabsorption of phosphate ion Albright and his associates[23] were subsequently able to prevent the sequelæ of parathyroid hormone administration on the urinary calcium and serum calcium by feeding phosphate and thereby preventing the fall in serum inorganic phosphorus

The evidence for the theory that the parathyroid hormone acts directly on bone is chiefly histologic Following the administration of this hormone marked osteoclastic proliferation in bone is observed However there are clinical evidences which are incompatible with this suggestion such as the fact that patients with active parathyroid tumors need not necessarily develop bone disease [14] The level of the serum inorganic phosphorus moreover is reduced in this disorder as well as following the administration

phosphorus does not exceed, and remains approximately constant at a value of 30 to 40. This indeed was the basis for the rule enunciated by Howland and Kramer[10] to the effect that in children where the *constant* ordinarily varies from 40 to 50, a reduction to less than 30 will result in rickets, and when the value exceeds 40, the disorder will heal.

Bone consists of mineral impregnated osteoid tissue. The latter consists of a protein ground substance composed chiefly of ossein and to a much lesser extent of osseomucoid and an albuminoid. Osteocytes, osteoblasts and osteoclasts are the cells normally located in the osteoid tissue. Approximately 80 per cent of the bone ash consists of $Ca_3(PO_4)_2$, 13 per cent of $CaCO_3$ and $Mg_3(PO_4)_2$ constitutes 2 per cent. The remaining 5 per cent is made up of K, Na, Cl, Fe and H. It has been suggested on the basis of x-ray diffraction patterns and refractive indices that the bone salts exist for the major part in the form of $n\,Ca_3(PO_4)_2 \cdot CaX_2$ or $CaCO_3 \cdot n\,Ca_3(PO_4)_2$ (dahllite).[11,12]

Bone may be formed either in an intramembranous or endochondral fashion but the essential processes are the same in both instances. Endochondral bone formation is characterized by a preliminary phase in which cartilage is broken down by osteoclasts and invaded by blood vessels. Subsequently osteoblasts lay down osteoid tissue which then becomes impregnated with bone salts. Intramembranous bone formation proceeds in the latter fashion without the preliminary cartilaginous phase. Fully developed bone therefore consists of mineral impregnated osteoid tissue laid down in circular pattern surrounding the vascular supply. Each pattern unit is referred to as a *Haversian System*. Osteocytes or bone cells are enclosed within bone. In areas where new bone is being formed osteoblasts may be observed in the periphery of the tissue while in regions of bone destruction osteoclasts are found. These latter cells resemble foreign body giant cells in appearance. The formation and destruction of normal bone goes on constantly and simultaneously. The nature of this dynamic equilibrium under normal circumstances is determined by a variety of factors such as the age of the individual, the physiological growth processes, nutrition, physical stress and strain, *etc.*

The function of the osteoblasts in the laying down of bone is a rather complicated one. These cells not only form the ground substance but also secrete *alkaline phosphatase*. The mechanism for the deposition of the mineral elements of bone is stilll not entirely settled. It has been hypothecated that calcium phosphate and the other bone salts are precipitated in the bony matrix because their solubility products are exceeded at the site of crystallization.[13] Albright[14] has suggested that the parathyroid hormone acts to maintain the serum concentration of calcium and of inorganic phosphorus at a level below their solubility product resulting in constant demineralization of bone. Nevertheless it has been presumed by this author as well as by others that mineral deposition continues because of a local increase in ions brought about by the presence of the enzymes *alkaline phosphatase*[15] and *phosphorylase* occurring at the site of calcification.[16] These enzymes then help liberate phosphate ions from organic sources. Phosphate thus being present in great excess, its calcium salt

salicylate and anhydrous acetic acid. Ross and Wood[39] found two components to the hormone, one with a molecular weight of 15 000 to 25 000, the other with a molecular weight of 500 000 to 1 000 000. The hormone is fairly stable in a slightly acid medium but is best preserved as a dry powder. It is stable to reducing agents but unstable to oxidizing agents. The U.S.P. XIV unit is defined as one hundredth of the amount necessary to increase the serum calcium in not less than ten dogs 8 to 16 kilograms in weight an average of 1 mgm. per cent within sixteen to eighteen hours after subcutaneous injection. More recently an assay method has been devised based on the fall of serum inorganic phosphorus in logarithmic proportion to the dose of parathyroid hormone administered.[31]

DISEASES OF THE PARATHYROID GLAND

Hypoparathyroidism.—Inadequate elaboration of the parathyroid hormone will result in hypoparathyroidism, the most overt manifestation of which is tetany. Although idiopathic hypoparathyroidism does occur, the most common cause of parathyroid insufficiency is the inadvertent removal or injury of the parathyroid glands occurring during the course of thyroid surgery. Postoperative hypoparathyroidism is encountered in approximately 1 per cent of the patients with Graves' disease subjected to thyroid surgery. In such instances the hypoparathyroidism may be either transient or permanent, depending upon whether the parathyroid bodies have actually been removed or subjected to injury from which recovery may take place. In contrast to the relative frequency of postoperative hypoparathyroidism is the rarity of the idiopathic variety.[54] In 1946 Leonard was able to collect only 35 such instances from the literature.[22,36] In those patients in whom pathologic examination was subsequently carried out, no parathyroid tissue was found or else the glands were completely replaced by fat.[2,36] The explanation for this form of parathyroid insufficiency is at present not apparent, particularly since no convincing evidence exists to link the parathyroids with the other endocrine glands.[36,44] On three occasions, however, Addison's disease has been encountered in conjunction with hypoparathyroidism.[36]

In addition to true idiopathic hypoparathyroidism it is possible that some instances of infantile tetany may fall into this category.[35] Pertinent to this consideration is the report of an infant with evidences of hypoparathyroidism born to a mother with hyperparathyroidism.[60] In this case a possible explanation resides in the demonstration that parathyroid hormone can pass the fetal barrier and that the injection of parathyroid hormone to the experimental animal may result in parathyroid hypoplasia.[65] In the human, however, it must be noted, atrophy of the remaining parathyroid glands is not found in association with the presence of a parathyroid adenoma.

Signs and Symptoms of Hypoparathyroidism.—The most obvious and overt manifestation of hypoparathyroidism is tetany, which in this disease is dependent on the associated hypocalcemia and the resultant increased neuromuscular excitability. The biochemical observations encountered in hypoparathyroidism consist primarily of a decrease in the urinary ex-

of parathyroid hormone in contrast to the high level which might be expected if this ion were constantly being liberated from bone.

The problem as to the mechanism by which parathyroid hormone exercises its effect could perhaps in part be elucidated by a study of the effects of this hormone in the bilaterally nephrectomized animal.[24] The results obtained in such preparations are partially obscured by the metabolic effects incidental to renal insufficiency. The majority of investigators have found that the administration of parathyroid hormone fails to induce an increase in the serum calcium in such animals.[14, 25] These results, however, have generally been obtained in those instances in which the serum phosphorus has been elevated. On the other hand, Ellsworth and Futcher[26] did report some elevation in the serum calcium level under these experimental conditions. Albright and Reifenstein[14] have pointed out that it is impossible to raise the serum calcium level with parathyroid extract in patients with renal insufficiency and resulting phosphate retention. These data by no means exclude the possible direct action of parathyroid hormone on bone. The fact that no elevation of serum calcium occurs following its administration in the nephrectomized animal and in the patient with renal insufficiency can at least theoretically be explained by the local precipitation of calcium occurring in the presence of a markedly elevated phosphorus. That parathyroid hormone does exercise some effect directly on bone is shown by the fact that its administration to the nephrectomized animal results in the production of the bony changes of osteitis fibrosa beyond those which could be explained on the basis of acidosis and renal insufficiency alone.[14, 7] It is probable that the hormone exercises its effects both by regulating the renal excretion of inorganic phosphorus and by its direct action on bone tissue. Recent studies by Tweedy and his associates[8] with radioactive phosphorus and by Barnicot[29] with transplants of parathyroid tissue and bone would tend to support the dual action of this hormone.

The administration of excessive amounts of parathyroid hormone to the experimental animal will result in dehydration, renal failure and death.[5] Shelling[52] has pointed out that in such experimental studies the characteristic features include a marked urinary diuresis with an increase in the urinary excretion of calcium, phosphorus and chlorides. There is an associated increase in the serum calcium level and a considerable reduction in serum sodium and chlorides. As the acute toxic state progresses, hemoconcentration becomes marked and extrarenal azotemia with a retention of nitrogenous products results. The animal becomes anuric and death finally ensues from acidosis, dehydration and circulatory collapse. At postmortem extensive calcification is found in the kidneys, blood vessels, gastric mucosa, bronchioles and perialveolar regions of the lungs. In general, metastatic calcifications are noted in those parts of the body where marked changes in pH occur.

The Chemistry of Parathyroid Hormone.—The parathyroid hormone is probably a protein according to available evidence.[4] It is soluble in water, saline, aqueous alcohol, 94 per cent acetic acid, concentrated warm phenol and in warm 50 per cent glycerol, but is insoluble in absolute ethyl, methyl or butyl alcohol, ether, benzene, pyridene, carbon tetrachloride, methyl

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below the zygomatic process. A positive sign consists of the contraction of the muscles of the upper lip on the tapped side of the alæ nasæ or of *the muscles of the eyelids. Any one or all three of these manifestations* may be present. *Trousseau's* sign is obtained by pressure upon the blood vessels and nerves of the upper extremity with sufficient pressure to stop the *circulation temporarily.* A positive sign is characterized by the production of carpopedal spasm. *Erb's* sign consists of an increased excitability of the motor nerves to galvanic current and for clinical purposes the cathodal opening contraction is the most useful of these electrical reactions. A contraction elicited with less than 5 milliamperes is usually pathognomonic of tetany. The *peroneal* or *Lust* sign consists of the mechanical stimulation of the peroneal nerve by tapping it at the lateral aspect of the fibula below the head. A positive test is evidenced by dorsal flexion and abduction of the foot. *This test has the same significance as the* Chvostek reaction.

Of interest is a recent observation by Engel and his associates[4] in which they *noted that if hypokalemia were associated with hypocalcemia tetany* resulted only when the level of the serum potassium was elevated following the administration of this ion.

Less characteristic manifestations of hypoparathyroidism include cataract formation and multiple ectodermal disorders such as dry scaly skin, absence of hair and atrophy of nails. Prompt and early treatment of hypoparathyroidism will prevent cataract formation, but once formed regression does not occur. Infrequently the multiple ectodermal disorders described above have been reported in association with idiopathic hypoparathyroidism.[39,40,41] More commonly such disorders are unrelated to diseases of the parathyroid bodies. Convulsive seizures, sometimes epileptiform in character, *may occur in hypoparathyroidism. Whether such epilepsy is the* result of hypoparathyroidism or represents true idiopathic epilepsy more readily precipitated by the hypoparathyroid state is a moot point.[11,33] In either event the successful treatment of the hypoparathyroidism will result in an amelioration of the convulsive seizures.

Gotta and Odoriz[42] conducted electroencephalographic studies in hypoparathyroidism. These investigators reported the presence of slow waves occurring 2 to 3 per second either singly or in series enhanced by hyperventilation but unaffected by the parenteral administration of calcium. The correction of the hypoparathyroid state results in a disappearance of the characteristic waves. In the associated presence of epilepsy the electroencephalogram may be entirely normal or show the presence of the slow waves, a generalized dysrhythmia, or both.

Rarely evidences of increased intracranial pressure and papilledema are observed.[38] *When these are associated with convulsion the diagnosis* of brain tumor may be mistakenly made. Symmetrical bilateral punctate calcifications in the region of the basal ganglia are commonly noted on *x ray examination of the skull.*[37] *These will not be affected by* successful treatment of the hypoparathyroidism.

The skeletal changes in hypoparathyroidism are generally slight. In adults the bones may show a mild *increase in density* although rarely

cretion of phosphorus, a rise in the level of serum inorganic phosphorus, a fall in the serum calcium level and a decrease in the urinary excretion of calcium. Since calcium is an important regulator of neuromuscular function the reduction of the serum level of this ion will result in characteristic manifestations. When the serum calcium falls to a critical level usually between 7 0 and 8 0 mgm per cent, some of the signs and symptoms of tetany may be elicited. When the serum level falls below this point the full blown clinical picture is encountered. The level of the total serum calcium however is not the sole determining factor in the production of tetany. This manifestation can be precipitated by alkalosis in the presence of a normal total serum calcium level and prevented by acidosis when the serum calcium is at a level low enough ordinarily to be associated with tetany. The explanation for these phenomena resides in the fact that changes in the pH of the blood alter the degree of ionization of calcium. Since the available ionizable calcium determines its physiologic activity the reduction of this fraction which occurs in alkalosis accounts for the occurrence of tetany even in the presence of a normal total serum calcium level. On the other hand the decrease in the pH of the blood occurring in acidosis will increase the available ionizable calcium. Finally the reduction in the total serum calcium which is so often found in hypoproteinemic states such as the nephrotic syndrome is infrequently associated with tetany. In such cases the available ionizable calcium is normal although that fraction ordinarily bound to protein is reduced.

The early manifestations of tetany consist of perioral paresthesia and numbness of the extremities followed by muscular spasms. Subsequently carpopedal spasm laryngeal stridor and generalized convulsions may ensue. Although tetany is seldom fatal the occurrence of laryngeal spasm may be of serious import. Shelling[2] described this manifestation well:

The most frequent symptoms of manifest tetany are carpopedal spasm laryngospasm and convulsions. . . . The second frequent sign of manifest tetany especially in children is laryngospasm. . . . the loud inspiratory crow is due to a spastic narrowing of the glottis. The spasm may be mild and may occur but infrequently or the attacks may follow in rapid succession and be accompanied by great difficulty in breathing cyanosis coma and death. In most instances however after a lapse of a few minutes and in spite of all signs of suffocation the spasm of the glottis relaxes air is heard entering the larynx and the cyanosis begins to disappear.

Spasm of both voluntary and involuntary musculature may be encountered. Tachycardia irregularities in cardiac rhythm and prolongation of the QT intervals on electrocardiographic studies are evidences of the effects of hypocalcemia on the cardiac musculature while abdominal pain nausea and vomiting point to the involvement of the musculature of the gastrointestinal tract.

At a serum calcium level of between 7 0 and 8 0 mgm per cent the clinical manifestations of tetany may not be overt. Under such circumstances evidences of tetany may be elicited by various tests. The more common of these include 1 Chvostek s sign 2 Trousseau s sign 3 Erb s sign and 4 the peroneal sign. The *Chvostek* sign is elicited by tapping the trunk of the facial nerve just anterior to the external auditory meatus or just

versibly with calcium ions such as oxalate and citrate and finally tetany may occur as a result of magnesium deprivation

An inadequate intake of calcium or a defect in the absorption of this element as occurs in steatorrhea or avitaminosis D may result in the infant in rickets or in the adult in osteomalacia In these syndromes a low serum calcium is associated with either a normal or a slightly reduced serum phosphorus The serum alkaline phosphatase is moderately increased as a result of the excessive deposition of osteoid which fails to become calcified

In *chronic renal insufficiency* although the serum phosphorus is high and the serum calcium is low the urinary findings, the elevated blood non protein nitrogen and the acidosis point to the underlying disease

Alkalotic tetany is usually easily differentiated by the presence of a normal serum calcium and phosphorus and a normal urinary excretion of these ions In *hyperventilation* the CO_2 content of the blood is reduced but the combining power is usually normal *If the alkalosis is the result of the ex* cessive ingestion of alkali the serum total base as well as the CO_2 combining power and content are increased

In alkalosis due to vomiting the CO_2 content and combining power are elevated the serum chlorides are reduced, while total base may be normal or slightly reduced

The Treatment of Hypoparathyroidism —The treatment of chronic hypoparathyroidism consists of the use of calcium salts and of either vitamin D or dihydrotachysterol (AT 10) The usefulness of parathyroid hormone is limited to acute hypoparathyroidism since refractoriness to the fraction may develop

In acute hypoparathyroidism such as occurs following thyroid surgery or the removal of a parathyroid adenoma the treatment of choice is the *use of parathyroid hormone intramuscularly and calcium gluconate intra* venously The former is given in dosages of 10 to 100 units a day either in one dose or in divided doses Its effect on the serum calcium level is observable within four hours and persists for approximately twenty to twenty four hours Unfortunately refractoriness to this hormone may occur within one to three weeks

In acute emergencies calcium may be repeatedly administered intravenously preferably as the gluconate in dosages of 10 cc of a 10 to 20 per cent solution When considering the oral administration of calcium it should be remembered that calcium is best absorbed in the presence of a low phosphate acid ash diet Consequently the chloride or the lactate or gluconate rather than the phosphate salts are usually employed Milk is to be avoided because of its high phosphate content Aluminum hydroxide may be used as an adjuvant in doses of 1 to 2 teaspoonfuls 3 times a day This drug combines with and precipitates the phosphate thereby facilitating the absorption of calcium

Vitamin D has a dual action it enhances the intestinal absorption of calcium and possibly aids in the deposition of bone and to a much lesser extent increases the renal excretion of phosphate Dihydrotachysterol (AT 10) has similar actions but its phosphate regulating effect is more pronounced and the antirachitic action less potent One may therefore

osteomalacia is found In infants if the disorder starts before dentition is complete, aplasia or hypoplasia of the teeth may result

Diagnosis of Hypoparathyroidism.—The diagnosis of hypoparathyroidism when suspected is established by the clinical and laboratory evidence of latent or manifest tetany including the Chvostek Trousseau, Erb and Lust signs and the characteristic biochemical alterations associated with this syndrome These are 1 a decrease in the serum calcium, 2 an increase in the serum phosphorus 3 a decrease in the urinary excretion of calcium and phosphorus, 4 a normal or decreased serum alkaline phosphatase When the serum calcium level is less than 7 to 8 mgm per cent calciuria is absent This may roughly and easily be determined by means of the Sulkowitch reagent

Differential Diagnosis—*Pseudohypoparathyroidism* and tetany due to causes other than true hypoparathyroidism must be differentiated from true hypoparathyroidism In 1942 Albright[46] and his associates described 3 patients presenting a syndrome clinically and biochemically similar to hypoparathyroidism who failed however to respond to the administration of parathyroid hormone Since then 7 other similar cases have been reported[45 49] These patients in addition to the usual clinical and biochemical features of hypoparathyroidism present certain characteristics Their physical appearance is similar in that all are short and thickset and have rounded facies In addition they have a tendency to brachydactyly especially of the metacarpals as a result of early closure of the epiphyses The metacarpals most likely to show shortening are those in which cartilage proliferation and epiphyseal formation are last to occur In some instances excessive soft tissue calcification is observed

The diagnosis is established by the observation that the administration of parathyroid hormone fails to induce an increase in the serum calcium a fall in serum phosphorus and an increase in the urinary excretion of calcium and phosphorus Two hundred units of parathyroid hormone are administered intravenously to the fasting patient The phosphorus content of the urine is measured hourly for periods of three hours prior to and five hours after the injection[45 47] Previous recent parathyroid hormone therapy must be excluded since refractoriness following the prolonged use of this fraction may normally occur This test is invalid in the presence of chronic renal disease since under such circumstances the urinary excretion of phosphorus may be impaired

Patients with pseudohypoparathyroidism respond equally well to either the administration of dihydrotachysterol (AT 10) or vitamin D[49] It seems likely that the therapeutic effect of these agents in this disease results from an increase in the intestinal absorption of calcium

The treatment consists of the use of either AT-10 or vitamin D in addition to the oral administration of calcium These measures are employed in the same dosage as is used in the treatment of true hypoparathyroidism

Tetany in general may result from hypoparathyroidism from an inadequate intake or absorption of calcium as in rickets osteomalacia and steatorrhea from alkalosis induced by bicarbonate ingestion vomiting or hyperventilation from the excessive rise in serum inorganic phosphorus as in renal insufficiency from the administration of drugs that combine irre-

uncommon. When more than two glands are involved it is probable that the underlying lesion is hyperplasia rather than tumor.[59]

In the series collected by Norris[57] the adenomata were equally distributed between the right and left glands but occurred far more commonly in the inferior group than in the superior parathyroid bodies, in a ratio of approximately 5 to 1. In 10 per cent of the cases the adenoma was found in an aberrant location. In almost two-thirds of this last group the tumor presented in the mediastinum and in slightly less than one-third the tumor was embedded in the thyroid. The remainder were found behind the esophagus.

The age distribution in general varied from ten to eighty years. The maximum incidence occurred in the group between forty and fifty years and 70 per cent occurred between the ages of thirty to sixty years. There was a marked predominance in females, the ratio to males being 3 to 1.

The tumors varied in size from 0.4 to 120 grams, the average weight being 12.5 grams. They were ellipsoid in most instances but some were bilobed. In general the tumors were yellowish brown or reddish brown in color, moderately soft, encapsulated and smooth. A rough quantitative proportion was found to exist between the size of the tumor and the degree of hypercalcemia.

Of interest are the reports of adenomatous enlargement of the parathyroids in conjunction with adenohypophyseal and pancreatic islet cell tumors.[61,62] The significance of such findings is at present not apparent, particularly since no definitive experimental demonstration of any functional interrelationship between these glands has been established.

Diffuse hypertrophy and hyperplasia of all the parathyroid glands causing primary hyperparathyroidism has been described.[64,59,53] Eight such instances were found in the 89 cases reported from the Massachusetts General Hospital.[14] In 1947, Rogers and Keating[60] reviewed 26 cases including 4 of their own. This type of primary hyperparathyroidism can generally be differentiated both clinically and histologically from the diffuse hyperplasia encountered in secondary hyperparathyroidism. The parathyroid cells in the former are large and water-clear, 10 to 40 microns in diameter, and often arranged in alveolar fashion, while in secondary hyperparathyroidism the cells are normal or slightly increased in size. In the series of primary hyperplasia reported from the Massachusetts General Hospital, the total weight of the parathyroids ranged from 20 to 160 times that of normal glands, varying from 2.5 to 19.0 grams.[14]

Carcinoma of the parathyroids is rare. In 1948 Norris[58] was able to collect only 15 cases which were acceptable as true malignant parathyroid tumors. Of these only 7 were endocrinologically active and resulted in hyperparathyroidism. More recently Black[63] reported another instance of a functional malignant parathyroid tumor.

The Bone Changes in Primary Hyperparathyroidism.—The bone changes in primary clinical hyperparathyroidism are almost identical with those observed in the experimental animal treated parenterally with parathyroid extract.[52,65] In general, the changes consist of a generalized decalcification of bone, a marked increase in the fibrous tissue of the bone marrow associated with the presence of increased numbers of osteoblasts and osteoclasts

employ either of these two compounds in the treatment of hypoparathyroidism. Vitamin D or calciferol (D_2) is given in doses of 50,000 to 300,000 international units daily. Dihydrotachysterol (AT-10) is administered in daily dosages of 3 cc. (3.75 mgm.) or 6 capsules each containing 0.625 mgm. until the presence of calcium is detected in the urine. The dosage is then reduced approximately to 1 cc. or 2 capsules 3 to 7 times a week. The use of the Sulkowitch reagent is of great value in adjusting the dosage, the proper dose being that sufficient to produce a moderate amount of calcium in the urine.

Hyperparathyroidism

Hyperparathyroidism results from hyperfunction of one or more of the parathyroid glands. This functional overactivity may be due to either diffuse hyperplasia of all of the parathyroids or more commonly a parathyroid tumor which is almost invariably benign. For both theoretical and practical reasons, it is important to distinguish these forms of primary hyperparathyroidism from secondary hyperparathyroidism such as may result from chronic renal insufficiency. Secondary hyperparathyroidism is always associated with diffuse hyperplasia of the parathyroid bodies.

Whatever the underlying pathologic cause of primary hyperparathyroidism, the physiologic and clinical sequelae are similar and resemble the effects induced by the exogenous administration of excessive parathyroid hormone. This is characterized primarily by the increased urinary excretion of phosphorus and calcium, a decrease in the level of the serum inorganic phosphorus, and an increase in serum calcium level. The clinical manifestations are dependent on these phenomena which result in a disease picture chiefly referable to the skeletal system and urinary tract, to the symptoms of parathyroid intoxication, or to various combinations of these.

The most common cause of primary hyperparathyroidism is a parathyroid adenoma. The comparative incidence of tumor and hyperplasia in this disorder is reflected in the number of cases of each reported in the literature. Primary hyperparathyroidism due to adenoma was recorded in 322[57] instances, carcinoma in 7[58,63] and diffuse hyperplasia in 27[60,64]. Of 104 cases in a series studied at the Massachusetts General Hospital, 84 were due to a single tumor, 7 to two adenomata, and 10 to diffuse hypertrophy. In this group 3 instances of carcinoma were also encountered.[94]

Parathyroid adenomata consist for the most part of chief or water clear cells.[3,14,59] Oxyphil adenomata have been reported in rare instances,[71] although the actual existence of such tumors is subject to some question.[3] However, in the adenomata encountered all three types of cells, chief, water clear, and oxyphil, may be present. The oxyphil or eosinophil cells are present in only small numbers.[3] This is in contrast to diffuse primary hyperplasia in which the sole cells found are large water clear cells.[14,60]

Norris[57] collected 322 cases of functioning parathyroid adenomata from the literature. He noted that in only 6.2 per cent was more than one parathyroid tumor found. In 12 of these, however, advanced renal disease was present. Albright and Reifenstein[14] also reported the incidence of multiple tumors in their series to be 6 per cent. Multiple tumors, therefore, are

that this type of fibrous alteration is a non specific reaction to rapid decalcification of bone This is readily demonstrated in the experimental animal where rapid decalcification induced by acidosis results in osteitis fibrosa similar to that which follows the administration of parathyroid extract[66] Finally nonspecific agents such as chloroform and lead acetate may produce similar changes[59 67]

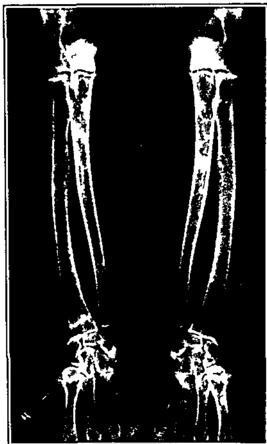


Fig 86 —Hyperparathyroidism Cystic area expanding the cortex in the base of the fourth right metacarpal bone There is a sharply demarcated calcific area in the lower end of the left ulna (Courtesy of Dr M Fieber)

The *giant cell tumors* which occur in primary hyperparathyroidism are neither malignant nor neoplastic These tumors which are sometimes referred to as osteoclastomas[68] or osteoblastomas [14] consist of boneless masses of soft tissue composed of osteoblasts osteoclasts and the supporting cells of the bone marrow They probably represent areas where the rapid and marked destruction of bone is associated with a local increase in the osteoclasts and osteoblasts Frequently these lesions are brown in color due to the presence of blood pigments resulting from the phagocytosis of red cells

the presence of bone cysts and giant cell tumors, and evidences of bone destruction and to a less marked degree of new bone formation The histologic characteristics of the bony changes have been summarized by Snapper as follows [39]

"1 Osteoclastic destruction of bone trabeculæ due to hyperactivity and accumulation of osteoclasts sometimes leading to formation of giant cell tumors

2 Decalcification of the remnants of bone trabeculæ

3 Apart from this osteoclastic decalcification and perhaps on account of it, generalized proliferation of fibrous tissue is found in the bone marrow and cortex—the osteitis fibrosa described by von Recklinghausen

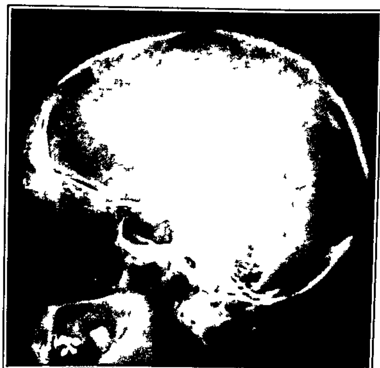


FIG 85 —Skull of patient with hyperparathyroidism Note localized areas of bone absorption and elevation of outer table over one of bony defects (Courtesy of Dr M Fieber)

4 The thinned bone trabeculæ are often perforated by the proliferating fibrous tissue, the so-called dissecting bone resorption

5 New formation of bone tissue as indicated by the proliferation of osteoblasts and the presence of osteoid seams

It is this last feature that accounts for the high serum alkaline phosphatase associated with these skeletal changes

It is now generally accepted that osteitis fibrosa is not pathognomonic of von Recklinghausen s disease This specific change is observed also in Paget's disease polyostotic fibrous dysplasia Graves disease renal ostiodystrophy, long standing acidosis and other disorders It would appear

Symptoms of Primary Hyperparathyroidism.—The symptoms and signs of hyperparathyroidism may include skeletal, renal and gastrointestinal manifestations in a variety of combinations. Not infrequently, however, the predominant clinical picture is referable to either the skeletal or the urinary system alone. Occasionally evidence of acute parathyroid intoxication is encountered.

The skeletal manifestations, usually referred to as *von Recklinghausen's disease*, are dependent on the marked negative calcium balance, as well as on the direct effects of parathyroid hormone on bone. The resultant decalcification and bony alterations result in indefinite skeletal pains which are often erroneously attributed to arthritis, bursitis, or, more loosely, neuritis. Bone tenderness is commonly found. Multiple pathologic fractures occur and deformities of the long bones, pelvis, and spine are thus produced. The x-ray is of particular value in von Recklinghausen's disease. "Although all the bones of the skeleton are involved, the effects are more pronounced in some areas than in others. In general, there is thinning and scalloping of the cortex, and widening of the marrow spaces. In addition, there is a porous appearance of bone due to dilatation of the Haversian canals, as well as decalcification and spontaneous fractures."[84] The compression and collapse of the softened vertebral bodies result in shortening of the patients and the appearance of fish bone biconcave vertebrae on x-ray examination. Bone cysts and giant cell tumors are frequently but not invariably present, and, as previously described, are most often noted in the bones of the skull or jaw, or zygoma, the metacarpals, metatarsals, and ends of long bones. The presence of such tumors and bone cysts is particularly significant in establishing the diagnosis. The roentgenologic appearance of coarsely meshed trabeculation and diffuse osteoporosis is often sufficient to strongly suggest the diagnosis. The clubbing of the fingers sometimes seen in this disease is associated with decalcification of the bones of the hand and fingers and absorption of the terminal phalanges.

Hyperparathyroidism is often first detected by the dentist, who may find an *epulis* of the jaw or an absence of the lamina dura of the teeth. The latter is of great significance, for when present it is indicative of a generalized osteoporosis.[84]

Marked polyuria and polydipsia are frequently observed in primary hyperparathyroidism. The polyuria appears to be greater than could be anticipated from the degree of hypercalciuria and hyperphosphaturia. The therapeutic and experimental administration of parathyroid hormone results in at least a temporary loss of water, inorganic base, and chloride, and when the hormone is withdrawn these substances are retained.[5] Following the successful removal of a parathyroid adenoma, temporary oliguria may occur.

The renal manifestations include *nephrolithiasis* and *nephrocalcinosis*, both of which have their origin in the alterations in the serum and urinary calcium. The former is dependent on the precipitation of calcium phosphate and oxalate stones as a result of the marked hypercalcemia. Stone formation is favored by urinary obstruction, infection, and an alkaline reaction in the urine. It has been reported that 3 to 5 per cent of all renal calculi are due to underlying hyperparathyroidism.[24,80,81] Repeated epi-

The most common locations for the giant cell tumors and bone cysts are the jaws and zygoma the metacarpals and metatarsals and the ends of long bones The *bone cysts* are probably degenerative in origin and are usually located at sites where previous trauma and hemorrhage have occurred It is questionable as to whether the cysts are the result of degenerative changes in giant cell tumors Following the successful treatment of primary hyperparathyroidism the giant cell tumors generally disappear while the cysts persist although they may undergo calcification



FIG 87 —Hyperparathyroidism Symmetrical areas of bone absorption in the shafts of the femora There is also a calcific semi circular shadow in the soft tissues of the medial aspects of the right femur The cortex in this area is sclerotic An inter medullary sharply demarcated calcification is present in the upper end of the left tibia (Courtesy of Dr M Fieber)

The bones which show the greatest degree of change are usually the long tubular bones particularly in the diaphyses and next in order of frequency the vertebral column pelvis skull jaw bones thoracic flat bones and the short tubular bones

Norris[37] has estimated that the average duration of the disease before the diagnosis is established is approximately 5 to 7 years although this obviously varies with the character of the manifestations and the index of suspicion of the physician

TABLE 31 —INCIDENCE OF SYMPTOMS OF HYPERPARATHYROIDISM FROM A SERIES OF 115 CASES COLLECTED FROM THE LITERATURE BY GUTMAN SWENSON AND PARSONS[79]

	Major Initial Symptom Percentage of Cases	*Major Late Symptom Percentage of Cases*
Skeletal		
Pain in the back or extremities	72	62
Muscle weakness	22	23
Pathological fractures	28	40
Bone swelling	26	22
Gross deformities	19	30
Disturbance of gait	24	22
Bedfast	4	31
Renal		
Polyuria Polydipsia	10	11
Colic	5	3
Gastrointestinal		
Nausea Vomiting	8	12
Anorexia	3	[illegible]
Epigastric pain	2	5
Miscellaneous		
Marked loss of weight	10	24

The Diagnosis of Primary Hyperparathyroidism.—The diagnosis is based essentially on the presence of the characteristic clinical skeletal and renal abnormalities and the presence of the typical biochemical changes The latter include an increase in the urinary excretion of phosphorus and calcium a decrease in the serum level of inorganic phosphorus an elevation in the serum calcium level and an increase in the serum alkaline phosphatase The serum calcium level is generally elevated above 11 0 mgm per cent and usually exceeds 12 mgm per cent Of the 114 cases collected by Gutman and his associates the serum calcium level was greater than 11 0 mgm per cent in 109 instances and exceeded 12 mgm per cent in 91 patients[8] In the series of 35 patients reported from the Massachusetts General Hospital 9 had serum calcium levels below 12 mgm per cent[14] It must be remembered that in the presence of renal insufficiency such as occurs in long standing cases of hyperparathyroidism and particularly when the serum inorganic phosphorus is increased the serum calcium level may be normal or even decreased[76]

Although the serum inorganic phosphorus concentration is usually reduced this is not invariably the case and it may even be increased in the presence of renal insufficiency Of a series of 79 proven cases of primary hyperparathyroidism in only a little less than half was the serum inorganic phosphorus level below 2 5 mgm per cent[59]

sodes of pyelonephritis and obstruction which so commonly occur in the presence of urolithiasis may result in renal insufficiency *Nephrocalcinosis* is due to both metastatic calcification resulting from the hypercalcemia and to the precipitation of calcium salts in the lumina of the renal tubules Calcification in the interstitium of the kidney particularly around the tubules is favored by the local changes in the pH The intratubular precipitation of calcium is similar in origin to that discussed for nephrolithiasis The diagnosis of nephrocalcinosis is based on the x ray detection of calcification within the renal shadow The presence of calcium casts in the urine is not pathognomonic of nephrocalcinosis but suggests the presence of hyperparathyroidism It should be emphasized that renal insufficiency may result from nephrocalcinosis even in the absence of x ray demonstration of renal calcification Early in the course of this disorder only the tubules are damaged later glomerular dilatation and impaired filtration occur In such instances following successful operation the glomerular function may return to normal but tubular function remains impaired

The question of the relative incidence of nephrolithiasis and of skeletal manifestations is an important one It is generally recognized that the predominance of the manifestations is to some extent determined by the daily dietary intake of calcium In the presence of a high calcium diet nephrolithiasis will more likely occur while in patients whose daily dietary intake of calcium is low skeletal manifestations will be more common

In the series studied at the Massachusetts General Hospital 52 of the first 62 cases observed had nephrolithiasis or nephrocalcinosis [14] In the same series only 35 had bone disease In the series of 322 cases collected by Norris [47] skeletal lesions alone were encountered in 60 per cent renal changes alone in 5 per cent and associated skeletal and renal manifestations in 31 per cent Involvement of neither system was found in 1 5 per cent It should be remembered that hyperparathyroidism must be present for a considerable period of time generally years before roentgen evidences of skeletal change are detectable On the other hand renal calculi form rather quickly As a consequence it might be expected that with earlier detection of the disease the relative incidence of renal manifestations will increase A possible explanation of the high incidence of renal complications encountered in this country is probably related to the high calcium content of the American diet [59] In Europe where milk is not an important adult food and the calcium intake in general low skeletal changes are more frequently encountered

Hypercalcemia results in decreased excitability of muscle in contrast to the hyperexcitability characteristic of hypoparathyroidism The clinical evidence of this is the marked hypotonia and decreased electrical reactions of skeletal muscle phenomena not uncommonly seen in these patients [73 74] The lack of tone resulting from this muscular effect of hypercalcemia affects the gastrointestinal musculature as well As a result anorexia constipation nausea and vomiting are not infrequent The electrocardiographic tracing shows a shortening of the Q T interval

The hypercalcemia may produce a peculiar band keratitis as well as deposits of calcium in the deep conjunctivæ of the palpebral fissure [75] while the marked osteitis fibrosa may result in anemia and leukopenia

phosphorus and calcium may be excessive; in the later stages the amounts excreted are considerably reduced. This is in contrast to what is generally observed in hyperparathyroidism, where in spite of marked demineralization of the skeleton excessive urinary loss of these elements continues. The skull is rarely involved in osteoporosis in contrast to hyperparathyroidism. A possible exception to this is the osteoporosis of Cushing's syndrome. Bone cysts and giant cell tumors are not found in osteoporosis and only rarely is the lamina dura absent. *Immobilization osteoporosis*, particularly in children, is clinically somewhat different from the osteoporosis of other etiologies. In immobilized patients the excessive liberation of calcium from bone results in an increase in the serum calcium level while the serum inorganic phosphorus remains normal or may even be slightly elevated. As in other instances of osteoporosis the serum alkaline phosphatase shows no change. Hypercalcuria is marked. When these patients are permitted activity, however, recalcification promptly occurs and the biochemical abnormalities vanish.

Albright and Reifenstein[14] have classified the causes of osteoporosis as follows:

- I. Defect in Osteoblasts
  - A. Loss of Stress and Strain
    - 1. Atrophy of Disuse
  - B. Lack of Estrogen
    - 1. Postmenopausal State
    - 2. Ovarian Agenesis
  - C. Congenital Osteoblastic Defect
    - 1. Osteogenesis Imperfecta
- II. Defect in Matrix
  - A. Loss of Androgen
    - 1. Eunuchoidism
    - 2. Senile Osteoporosis
  - B. Loss of Protein
    - 1. Malnutrition
    - 2. Hypovitaminosis C
    - 3. Cushing's Syndrome
    - 4. Alarm Reaction
- III. Effect Unknown
  - A. Acromegaly
  - B. Idiopathic Osteoporosis

In *osteomalacia* and *rickets* there is generalized decalcification and absence of the lamina dura, but tumors and cysts are rarely found. The deformities encountered in osteomalacia and rickets are due to bowing of the weakened bones rather than to true fractures. Pseudofractures do, however, occur in that form of osteomalacia known as "*Milkman's Syndrome*," which is due to avitaminosis D. In rickets and in osteomalacia the concentration of the serum inorganic phosphorus is reduced, while the alkaline phosphatase is elevated. These laboratory findings are similar to those observed in hyperparathyroidism. In the former disease, however,

The demonstration of an increase in the urinary excretion of calcium and a negative calcium balance is significant in establishing the diagnosis of hyperparathyroidism in suspicious cases. Under normal circumstances 70 to 90 per cent of the daily calcium intake is accounted for in the stool and only 10 to 30 per cent is excreted in the urine. In hyperparathyroidism this relationship is reversed and this fact may be utilized for the diagnosis. The patient is placed on a low calcium diet containing approximately 100 mgm a day for 2 successive three-day periods. On this regimen, the daily urinary calcium excretion will not exceed 100 mgm in normal subjects. The daily urinary excretion of 150 mgm or more is suggestive of hyperparathyroidism.[9] Hypercalciuria may be absent in the presence of renal insufficiency or if hyperparathyroidism is complicated by coexistent avitaminosis D.[69] A rough clinical guide for the presence of hypercalciuria is afforded by the use of the Sulkowitch reagent. A heavy fasting urinary precipitate is suggestive of hypercalciuria and hence hypercalcemia.

Where skeletal manifestations are prominent and there is active deposition of osteoid and bone, the serum alkaline phosphatase is usually elevated above 12.0 King-Armstrong units and above 5.0 Bodansky units in adults.[77, 9] However, in the absence of skeletal changes this finding may be normal. This determination is therefore best employed as an index of new bone formation rather than a diagnostic criterion of hyperparathyroidism, since it may not be increased in this disease and is increased in a variety of other bone diseases in which active new bone formation takes place. The finding of a normal serum alkaline phosphatase value in the presence of roentgen evidence of bony changes is a strong point against the diagnosis of hyperparathyroidism.

Differential Diagnosis.—Hyperparathyroidism must be differentiated from (1) skeletal lesions which mimic it, (2) other causes of hypercalcemia, and (3) renal lesions resulting in calculi, nephrocalcinosis and renal insufficiency.

The confusing skeletal lesions include *osteoporosis* from any cause, *osteomalacia* and *rickets*, *osteogenesis imperfecta*, *polyostotic fibrous dysplasia*, *Paget's disease*, *solitary bone cyst*, *multiple myeloma* and *metastatic malignancy*. Other bone diseases less likely to be confused with hyperparathyroidism include *lymphoma*, *Gaucher's disease*, *xanthomatosis*, *chronic radium poisoning*, *benign metastasizing hemangioma* and *renal osteitis fibrosa generalisata*. The chief causes of hypercalcemia which must be distinguished from hyperparathyroidism are *hypervitaminosis D*, *Boeck's sarcoidosis* and hypercalcemia resulting from the excessive ingestion of milk and alkali.

The important renal syndromes which may be confused with hyperparathyroidism are those producing nephrocalcinosis such as lower nephronephrosis resulting in renal acidosis, the secondary hyperparathyroidism of renal insufficiency and the syndrome due to immobilization.

Osteoporosis not due to hyperparathyroidism is distinguished by several features. Except for the osteoporosis resulting from immobilization, the serum calcium and phosphorus levels are within the normal range and since no new bone is formed the serum alkaline phosphatase is not increased. Although early in the course of the osteoporosis the urinary excretion of

have been reported In multiple myeloma the serum alkaline phosphatase is rarely if ever elevated and in the presence of bone disease is a strong point against the diagnosis of hyperparathyroidism The presence of Bence-Jones protein in the urine an increase in the serum globulin content and the identification of myeloma cells on sternal marrow aspiration serve to establish the diagnosis of multiple myeloma

Metastatic malignancy is readily differentiated from primary hyperparathyroidism In the former the lesions are sharply demarcated within otherwise normal bone Occasionally diffuse decalcification occurs The concentration of serum calcium may be elevated and hypercalciuria and nephrolithiasis result The concentration of the serum phosphorus however is usually normal occasionally increased and but rarely decreased The serum alkaline phosphatase may be increased in the presence of osteoblastic types of metastases The more likely sources of the primary lesions are the breast prostate kidney bronchi and thyroid gland

Hypervitaminosis D may result in metastatic calcification and the clinical manifestations associated with hypercalcemia including polyuria, polydipsia and impaired renal function The distinction from hyperparathyroidism is based on the history of prolonged ingestion of large amounts of vitamin D

In *Boeck s sarcoidosis* hypercalcemia [53] hypercalciuria nephrolithiasis a high serum alkaline phosphatase and bone lesions have been reported [53] The serum inorganic phosphorus however is not reduced and hyperproteinemia and hyperglobulinemia are almost constant findings Generalized lymphadenopathy is frequently present Further aid in the differentiation from hyperparathyroidism is provided by the facts that the bone lesions in sarcoidosis are usually confined to the hands and feet and generalized demineralization is not observed Finally the diagnosis of Boeck s sarcoidosis may be established by a positive Nickerson Kveim test and the characteristic histologic appearance of biopsied tissue

The excessive and prolonged intake of milk and alkali have been reported to produce a syndrome characterized by 1 hypercalcemia without hypercalciuria 2 a normal or elevated serum phosphorus level 3 impaired renal function with retention of non protein nitrogen and occasionally with nephrocalcinosis 4 conjunctival calcium deposits and band keratitis and 5 the clinical improvement which follows the decrease in the serum calcium level resulting from a decreased calcium intake [14 55]

Nephrocalcinosis resulting from hyperparathyroidism must be differentiated from other causes of renal calcification such as lower nephron nephrosis hypervitaminosis D and more rarely renal tuberculosis and chronic diffuse glomerulonephritis [14 56]

Treatment of Primary Hyperparathyroidism —The treatment of primary hyperparathyroidism consists of the surgical removal of the underlying parathyroid adenoma or resection of sufficient parathyroid tissue in those instances due to diffuse hyperplasia

Dietary therapy is of little value in the treatment of this disease A high calcium diet will decrease the negative calcium balance and thereby spare the skeleton but will also serve to increase the urinary excretion of calcium and thus favor the development of renal complications Since

both the serum calcium level and the urinary excretion of calcium are depressed, in contrast to that in hyperparathyroidism

Osteogenesis imperfecta sometimes loosely referred to as "brittle bones" is easily differentiated from hyperparathyroidism. It is an hereditary disorder associated with blue sclerae and multiple fractures beginning in very early infancy. The fractures surprisingly occur through the thickest rather than the thinnest portions of bone. When the disease is detected later in life *x* ray studies reveal a thin but not decalcified skull and an intact lamina dura of the teeth. The serum alkaline phosphatase may be elevated but the serum calcium and phosphorus levels, as well as the urinary excretion of these ions are within the normal range.

Polyostotic Fibrous Dysplasia is characterized by 1 a disseminated but not generalized osteitis fibrosa usually of segmental distribution 2 precocious puberty especially in females and 3 cutaneous pigmentation. It is differentiated easily from hyperparathyroidism by the facts that in the former disease (*a*) the uninvolved areas of bone are completely normal, (*b*) the lesions are hyperostotic as well as hypoostotic, and (*c*) the serum concentrations of calcium and inorganic phosphorus are normal, although the serum alkaline phosphatase may be elevated. There is no increase in the urinary excretion of calcium.

Solitary bone cysts are particularly apt to occur at the ends of long bones and often lead to pathologic fracture. Although they are histologically indistinguishable from those seen in hyperparathyroidism and in polyostotic fibrous dysplasia they are not accompanied by any other evidences of disease.

Paget's disease may be a localized or disseminated process and has as its sites of predilection the lumbar spine pelvis femurs clavicles tibias and skull. In this disease the architecture of the new bone is abnormal and the cortex is thickened. Marked thickening of the periostium and diffuse swelling of those bones which are involved is common. Bone cysts and giant cell tumors are rarely if ever seen and the involved bones are non tender. This is in contrast to the thin cortex normal architecture the localized swelling of cysts and giant cell tumors, and the bony tenderness observed in von Recklinghausen's disease. Hypercalciuria and nephrolithiasis may occur in Paget's disease but these are relatively uncommon. The serum concentrations of calcium and inorganic phosphorus are normal but the serum alkaline phosphatase may be inordinately elevated.

Multiple myeloma is characterized by the presence on *x* ray examination of multiple sharply demarcated punched-out lesions. These are especially significant if localized to the skull but may also be seen in the pelvis ribs spine, and long bones. Not infrequently it may be difficult to differentiate this disease from hyperparathyroidism since diffuse decalcification of the skeleton frequently occurs. In approximately 10 per cent of the patients with multiple myeloma the serum calcium level may be elevated and in such instances the urinary excretion of this ion is increased and nephrolithiasis may occur. Myeloma kidney may follow the deposition of protein in the renal tubules. Chronic renal insufficiency and secondary hyperparathyroidism result. Indeed two instances of parathyroid hyperplasia in patients with multiple myeloma and hypercalciuria and azotemia

depleted bone. As a consequence the tetany may be severe and the low serum calcium is accompanied by a low serum phosphorus. In such patients there is a rough parallel between the initial height of the serum alkaline phosphatase and the severity of the subsequent postoperative tetany. The serum alkaline phosphatase rises during this period and may stay elevated until recalcification is completed, often a matter of many months or longer.

The treatment of acute postoperative tetany is essentially similar to that described elsewhere in this chapter for the treatment of hypoparathyroidism. This consists of the oral and intravenous use of calcium salts and injections of parathormone. Where the tetany is more persistent and prolonged, dihydrotachysterol (A.T. 10) or vitamin D is substituted for parathormone, since refractoriness to this develops. Tetany associated with postoperative recalcification of the skeleton is apt to be both persistent and refractory despite the usual therapeutic measures. In such instances calcium must be vigorously administered through every available route in an attempt to provide adequate amounts of this ion both for skeletal repairs and for other physiologic needs. Vitamin D is given to aid absorption. The daily injection of 100 units of parathyroid hormone in 2 or 3 divided doses is later followed by the oral administration of dihydrotachysterol.

Secondary Hyperparathyroidism.—Diffuse hyperplasia of the parathyroid glands may result from calcium deprivation, rickets and osteomalacia, biliary fistulae and chronic jaundice,[89] pregnancy and lactation, multiple myeloma, and finally chronic diffuse glomerulonephritis or chronic pyelonephritis.[92] When this type of enlargement of the parathyroid glands is associated with skeletal changes similar to those seen in primary hyperparathyroidism, the clinical syndrome is referred to as "secondary hyperparathyroidism." The parathyroid glands observed under such circumstances are histologically different from those seen in primary hyperparathyroidism.[3] In the former the glands are enlarged and are made up of all three cellular elements. In most instances, however, the chief cells are predominant, although in some cases the water-clear cells are more numerous. There is an absence of mitoses and a decrease in or absence of intercellular fat tissue. In addition, the glycogen content of the cells is higher than is found either in adenoma or in primary hyperplasia of the parathyroids.[3] The usual size of the water-clear cells characteristic of primary hyperplasia renders the histological differentiation relatively simple.

The recognition of secondary hyperparathyroidism is of importance, since in this condition no cure can be envisaged, while in primary hyperparathyroidism surgical intervention may result in considerable improvement and often in cure. On the other hand, instances of primary hyperparathyroidism resulting in renal disease, renal insufficiency, followed by secondary hyperparathyroidism have been reported.[8, 90]

The clinical syndrome of secondary hyperparathyroidism, in contrast to simple secondary parathyroid hyperplasia, is almost invariably associated with chronic renal insufficiency with acidosis. Under these circumstances the retention of organic and inorganic acids by the insufficient kidney results in phosphate retention and acidosis. Parathyroid hyper

these renal manifestations are serious features of the illness, a low calcium diet is preferable Initially a high calcium diet will increase the hyper calcemia and the symptoms dependent on the elevated serum calcium level A high phosphorus diet will raise the level of the serum inorganic phosphorus and depress the serum calcium concentration However the increase in urinary excretion of phosphorus will favor precipitation of calcium phosphate A low calcium and low phosphorus diet is therefore desirable while the patient awaits operation

Some favorable results have been said to follow the use of x ray therapy to the parathyroid bodies [87,88] The evidence, however, is dubious and most observers doubt the efficacy of this form of treatment This therapy should be avoided and surgery resorted to without any undue waste of time

Before operation an attempt should be made by suitable x ray studies to locate the site of a possible parathyroid tumor Search should be par ticularly directed to the esophagus and mediastinum, employing esophograms and tomographic studies In approximately 10 per cent of the cases, such tumors may be located preoperatively [94] Surgical exploration is carried out bearing in mind that most tumors arise from the inferior para thyroids However if no tumor is located in the usual sites the exploratory procedure is incomplete unless the mediastinum is carefully searched

Where primary hyperparathyroidism is due to diffuse hyperplasia of the parathyroid glands rather than to a discrete tumor the procedure of choice is the removal of three parathyroid bodies and the subtotal resection of the fourth At least 200 mgm of viable gland tissue with an adequate and uncompromised blood supply are left behind

After operation the serum calcium level drops promptly and may reach normal levels within twenty four to thirty-six hours The greater the ini tial serum calcium concentration the greater is the likelihood that symp-toms of tetany will occur postoperatively Within thirty-six to forty-eight hours after operation the serum calcium level often falls below the normal range and the signs of low calcium tetany become evident Failure of the serum calcium level to fall is indicative of the presence of another tumor if one has been removed or in the case of diffuse hyperplasia of inade-quate resection With the decrease in serum calcium concentration the urinary excretion of this ion is diminished but at a somewhat slower rate This is clinically evidenced by the fact that patients with overt tetany may continue to excrete calcium in the urine for two to three days after operation By the fourth postoperative day however calcium is usually no longer detectable in the urine

Postoperative tetany generally falls into three categories The first is transient in character and is dependent on the functional inactivity of the remaining parathyroid tissue This form of tetany lasts for approxi mately a week The second form encountered is that associated with chronic hypoparathyroidism due to excessive removal of parathyroid tissue The treatment is dependent on the severity of the disorder and is outlined under the previous discussion of hypoparathyroidism Finally a refractory form of tetany may be observed in patients with hyperparathyroidism and severe skeletal changes In this group calcium and phosphorus are con stantly being withdrawn from the serum for recalcification of the markedly

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plasia then occurs as a result of the fall in serum calcium brought about by the rise in serum inorganic phosphorus. Associated with the parathyroid hyperplasia are skeletal changes. This entity is often referred to as "*renal hyperparathyroidism*" or "*renal rickets*" or "*renal osteodystrophy*". When this syndrome occurs in the adult, it is characterized by a generalized osteitis fibrosa which is identical with that observed in patients with primary hyperparathyroidism; however, bone cysts or giant cell tumors are not seen. In children, in addition, epiphyseal changes are noted, where no such changes are seen in primary hyperparathyroidism. These epiphyseal changes, which on roentgenologic study resemble true rickets, are histologically quite different.

In *renal osteodystrophy* in the child, the roentgenograms may reveal large and deeply cupped metaphyses with a wooly appearance. The distal ends of the diaphyses show irregular metaphyseal margins and a well-defined epiphyses peripherally. Epiphyseal slipping frequently occurs because of the generalized decalcification and subperiosteal erosion of the metaphysis. In general the porous appearance and transparency of the bones is much greater than in true rickets. These changes are best noted in the knees, wrists and ankles. In addition there is a moth-eaten appearance associated with decalcification and stippling noted in the skull. Whether the skeletal changes in this syndrome result from renal acidosis alone or are due actually to an increase in secretion of parathyroid hormone is a disputable point. The probable significance of the latter is suggested by the fact that the administration of parathormone to nephrectomized animals results in a degree of skeletal change considerably greater than that observed in untreated nephrectomized controls.[14] It is interesting to note that nephrectomized parathyroidectomized animals fail to develop skeletal changes.[77]

The clinical features of the disease are renal insufficiency with fixation of the specific gravity, an increase in the blood non protein and urea nitrogen levels, a decrease in the CO_2 content of the blood, an elevation of the inorganic phosphorus of serum and a normal or slightly reduced serum calcium level. The serum alkaline phosphatase is usually elevated. Calcium may be deposited about the joints in the skin and arteries and in the latter may produce *Monckeberg's sclerosis*.

The differentiation from primary hyperparathyroidism may at times be difficult, since renal disease associated with this latter syndrome is often extensive enough to produce renal insufficiency, in which case the serum inorganic phosphorus may rise and the serum calcium fall.

The treatment of secondary hyperparathyroidism is directed essentially towards control of the acidosis and the symptoms referable to the skeletal changes. The regimen consists of a high calcium, low phosphorus diet with added vitamin D. Alkaline salts, such as sodium citrate, given orally in a dosage of 8 grams a day will serve to correct the acidosis and to decrease the negative calcium balance. On this regimen the skeletal changes may be considerably improved.

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Section VI Hypoglycemia, Hyperinsulinism and Diabetes Mellitus

Chapter 30

ANATOMY AND PHYSIOLOGY OF PANCREATIC ISLET TISSUE AND THE PATHOGENESIS OF DIABETES MELLITUS

THE NORMAL PANCREAS THE PANCREAS IN DIABETES MELLITUS EXPERIMENTAL DIABETES MELLITUS AND PATHOGENESIS OF DIABETES MELLITUS IN MAN

BY HENRY DOLGER M D

The Normal Pancreas—The pancreas normally presents a wide range in size histology and insulin content Few organs of the body are less constant in size and architecture[13] The weight varies from 60 to 160 grams averaging about 95 grams Such fluctuations depend upon the amount of fat present which reflects the state of nutrition of the individual

The acinar cells and the duct system although constituting the bulk of the gland play no role in insulin secretion and therefore will not be discussed The *islets of Langerhans* are composed of anastomosing short cords 1 to 2 cells thick without encapsulation and have an average diameter of 70 to 150 micra[14] Individual islets may vary from a single cell to large groups of over 300 micra in diameter The total number of islets in the human pancreas also varies considerably with 500 000[14] to 1 000 000[14] considered as the average They constitute about 3 per cent of the pancreas by weight and volume After the third year of life the number of islets remains constant but their weight and volume increase with age Although distributed throughout the pancreas the greatest concentration of islets is found in the tail of the gland[15] An extraordinarily rich blood supply with a rapid flow courses through wide anastomosing sinusoids within the islets

Specific granulation demonstrable by differential staining distinguishes the islet cells from those of the acini and ducts Two types of islet cells are commonly recognized the alpha and the beta A third type the *D* cell is thought to be a transition form due to aging of the alpha cell[14] In human islets the alpha cells tend to nestle along the capillaries while the beta cells occupy the less vascular areas Beta cells outnumber alpha cells normally constituting 60 to 90 per cent of the islets while alpha and *D* cells make up the remainder Considerable degranulation especially of the beta cells is a common finding even under apparently normal conditions Insulin is produced by the beta cells The function of the alpha cells was

not apparent until recent investigations indicated these cells to be the source of a hyperglycemic factor [17] to be discussed later

The Pancreas in Diabetes —Since 1788 when Thomas Cawley[18] reported the autopsy findings of pancreatic calculi in a patient dying of diabetes mellitus the pancreas has been associated in an etiologic sense with diabetes One hundred years later von Mering and Minkowski[19] in successfully performing total pancreatectomy in the dog established this relationship by the production of a syndrome analogous to diabetes in the human being In 1901 Opie[16] noted what for quite a few years came to be accepted as a specific diabetic lesion, namely hyalinization of the islets Further elucidation of the problem seemed at hand with Allen s[20] finding hydropic degeneration in the beta cells of *dogs* rendered diabetic by a combination of subtotal pancreatectomy and high caloric feeding The more recent demonstrations of beta cell degeneration following the administration of alloxan,[1] anterior pituitary extract,[22] and glucose continuously [23] unfortunately have been limited to the experimental animal

In human diabetes however the pathologic lesions in the pancreas afford no basis for the anatomic diagnosis of the condition, differing *only in frequency* from identical changes observed in non-diabetic individuals [12] The anatomic causes of insulin deficiency are

1 Selective destruction of islet cell tissue
2 Inadequate blood supply to the islets (arteriosclerosis)
3 Widespread destruction of pancreatic tissue as in pancreatitis carcinoma and hemochromatosis

The last being understandably equivalent to surgical pancreatectomy, requires no elucidation particularly in view of the rare incidence of these organic lesions in diabetic patients

Variations in the islets of Langerhans may be quantitative or qualitative An apparent *decrease* in the number of islands is noted in *only 20 per cent* of diabetic patients on postmortem examination the normal number being found in 80 per cent [13] Analysis of the weight of the gland reveals a similar approximation to that of the normal pancreas in 67 per cent of Warren s series of diabetic autopsy material [13] Occasionally the complete absence of demonstrable islets may be found *without* any clinical evidences of diabetes [24]

Certain qualitative degenerative changes such as hyalinization fibrosis and lymphocytic infiltration of the islets along with such cytologic alterations as hydropic vacuolation have been considered fairly typical of diabetes Yet in a great many instances where severe diabetes had been present during life autopsy examinations have revealed apparently *normal* islets [14] In fact not infrequently hypertrophy of the islets has been noted [13]

Hyalinization of the islets first described fifty years ago as the specific lesion in diabetes was found in only 41 per cent of Warren s cases [13] and then almost exclusively after the age of forty In patients *without* diabetes this lesion has been found in 10 to 16 per cent of cases over fifty years of age [5-6]

Fibrosis of the islets was noted in 27 per cent of Warren s diabetic series compared with 7 5 per cent of non-diabetic cases [13] and 11 4 per cent of patients with essential hypertension [6]

The increased incidence of hyalinization and fibrosis with old age in both diabetic and non-diabetic individuals and the extreme rarity of these

lesions in young diabetic patients would indicate that no causal relationship exists between these anatomic findings and the syndrome. The accelerated aging which appears to be an integral part of the clinical picture of diabetes probably accounts for the increased incidence of the nonspecific lesions. Moschcowitz[4] believes that progressive *capillary sclerosis* leads to fibrosis and eventual hyalinization of the islets. He considers the latter to be related to the duration rather than severity of diabetes. He noted a two-fold increase in these islet lesions among *hypertensive*-diabetic patients as compared to diabetic individuals *without* hypertension.

Lymphocytic infiltration of the islets is found only among diabetic children and in these to an extent of less than 20 per cent.[13]

Hydropic degeneration or vacuolation, common in the experimental diabetic animal, is infrequent in the human diabetic patient (4 to per cent[13]). Gomori[14] believes this lesion expresses acute strain of carbohydrate metabolism, finding it in biopsy specimens of the pancreas obtained from 5 individuals receiving large amounts of glucose preoperatively.

Degranulation of the beta cells is pronounced in 25 per cent of human diabetic pancreases, according to Bell.[7] Some reduction in granulation is noted in another 35 per cent, while no alteration of the beta granulation can be found in 40 per cent. Only *insulin concentration* of the beta cell is indicated by its granulation. A *degranulated* beta cell may represent *either* increased activity and liberation of insulin or reduced activity. The histologic finding of a decreased number of Golgi bodies in the beta cells is the only indication of *reduced cellular activity*.[14]

In general, none of the pathologic lesions in the pancreas can be correlated with the clinical syndrome of diabetes mellitus in the human being. The histologic findings are not diagnostic, but only suggestive of diabetes.

The Insulin Content of the Normal and Diabetic Pancreas.—Since diabetes mellitus represents an *insulin insufficiency*, either of *absolute* or *relative* nature, study of the functional dynamics of the islets would seem to offer more promise than the unrewarding investigation of anatomic lesions just described. Unfortunately, very few observations on islet physiology relate to human diabetes. The mass of evidence accumulated so far, some of it conflicting, is derived mainly from animal observations.

Both the concentration of insulin in the beta cells of the islets and the total volume of beta cells must be considered in estimating the insulin content of the pancreas. Either of these two values may be altered by the various factors which effect the insulin content of the pancreas. Studies on the partially depancreatized but *non-diabetic* dog indicate that the concentration of insulin in the beta cells is more significant than the total content.[23] Although the operation reduces the total content by the loss of a fairly large amount of pancreatic tissue, the normal insulin concentration in the remnant of gland is sufficient to prevent the appearance of diabetes. Estimates of the insulin content of the pancreas reveal little of the underlying mechanisms involved, since a reduction in the content may result from either an increased release or liberation of insulin, or a decreased production of insulin, or both.

The standard reference for the *insulin content* of the *human pancreas* has been the work of Scott and Fisher.[9] These observers determined the

insulin and zinc content of the pancreas obtained at autopsy of 14 normal individuals who met almost instantaneous death as a result of accidents or other causes. Another series of glands was obtained at autopsy from 18 individuals with a history of diabetes mellitus of some years duration all of whom had received insulin daily. The primary cause of death in the latter group was not diabetes but rather acute and chronic conditions ranging from pneumonia to sepsis, cardiac failure and carcinomatosis.

The *average value* obtained for the insulin content of the pancreas of *normal* individuals was *1.7 units per gram* of tissue, a figure identical with that of the cat and cow. The lowest value in this group was 0.6 units per gram, in a case of alcoholic poisoning.

The *average value* obtained from the pancreas of the *diabetic* patients was only one-quarter that found in the normal group, *0.4 units per gram* of tissue. Although most of the pancreases contained between 0.1 and 0.5 units of insulin per gram, the lowest values (0.08 and 0.03 units per gram) were obtained from the 2 patients who had received large amounts of insulin (100 to 200 units) before death. A question arises as to whether the marked reduction in these 2 patients did not reflect the effect of insulin administration and fasting, both of which reduce the insulin content of the pancreas in rats.[30,31]

An unexplained but provocative finding was that of a *normal* insulin content (1.9 units per gram) in the case of a seventy-six year old woman with a moderately *severe diabetes* for many years. The condition had been fairly well regulated with insulin. The cause of death was extreme arteriosclerosis, fibrosis of the myocardium and acute aortitis.

Some doubt as to the validity of the above determinations has been expressed by Franklin and Lowell.[3] In their attempt to obtain a quantity of human insulin for an experimental study of insulin resistance some 50 pancreases were extracted. These were obtained from patients dying of various subacute and chronic diseases with the *exclusion of diabetes*, sepsis and tuberculosis. They found an average yield of 0.6 units per gram which when corrected by the factor necessary to approximate Scott and Fisher's technic resulted in a *normal value of 0.84 units per gram*. Apparently the striking difference noted by Scott and Fisher between the insulin content of the pancreas from diabetic and non-diabetic individuals was exaggerated by the presence of associated debilitating diseases in the diabetic group.

Factors Influencing the Insulin Content of the Pancreas in the Experimental Animal.—In young rats the insulin content of the pancreas, the activity of the beta cells and the volume of the islets are all *reduced* by (1) *insulin* administration,[30] (2) *starvation* or undernutrition[31] and (3) *high fat* or low carbohydrate intake.[31,34] These changes are not influenced by removal of the pituitary or adrenal glands and a recovery to the normal state occurs upon cessation of the experiment.

Factors *increasing* islet growth and insulin concentration in young rats include (1) injection of *anterior pituitary extracts*,[35] 2) administration of desiccated *thyroid*,[36] 3) *high carbohydrate diet*,[31] and 4) continuous or repeated injection of *glucose*.[37] However, the *secretion* of insulin by the isolated perfused rat pancreas in response to a high blood sugar level is suppressed

by anterior pituitary extracts[38] In general rats are extremely resistant to the production of experimental diabetes

In dogs, fasting and fat feeding do *not* affect the insulin content significantly[39] The injection of crude anterior pituitary extracts or purified growth hormone causes marked degenerative changes in the beta cells with reduction of insulin content to extremely low levels[72] Similar changes occur following the administration of purified growth hormone to normal cats[105] In this species however, crude anterior pituitary extract is effective only after partial pancreatectomy[40] Naturally the toxic necrosis of the beta cells following alloxan administration results in a marked reduction in pancreatic insulin in most animals[41]

EXPERIMENTAL DIABETES MELLITUS

Diabetes mellitus has been produced in man and animals by one or more of the following procedures

1 Total pancreatectomy (man and most animals)
2 Subtotal pancreatectomy alone or in combination with
   a) high caloric intake (cat dog)
   b) prolonged insulin administration (dog)
   c) injection of either crude anterior pituitary extract or purified growth hormone (cat dog)
   d) thyroid administration (dog)
3 Crude anterior pituitary extract or purified growth hormone administration (dog cat)
4 Adrenal cortical steroid administration (rat man)
5 ACTH administration (man rat)
6 Estrogen administration (rat)
7 Alloxan (man[9] most animals)
8 Glucose administration
   a) parenterally (cat)
   b) forced feeding (rat)

The application of these procedures to the clinical syndrome of diabetes mellitus in man can be limited to total pancreatectomy and the administration of alloxan anterior pituitary extract ACTH and adrenal cortical steroids That such induced diabetes involves organs and systems *other* than the pancreas was first demonstrated in the Houssay animal Houssay and Biasotti[42] removed the pituitary of the depancreatized dog whereupon the diabetes disappeared recurring with the administration of anterior pituitary extract Similar alleviation of the diabetic syndrome in the alloxan treated animal follows hypophysectomy[43] Removing the adrenal glands[44] and to a lesser extent the thyroid[45] in depancreatized animals also produces an amelioration of diabetes Pituitary extract is ineffective as a diabetogenic agent in fasted fat fed or insulin treated animals[38]

The contradictory diabetogenic effects of crude anterior pituitary extract (or growth hormone) can be summarized as follows

Dogs	No diabetes in puppies, only increased growth. Severe diabetes in adult animals requiring more insulin than depancreatized dogs
	Survive without insulin and maintain weight on high protein diet
	Some dogs entirely resistant even to massive doses
Cats	Diabetes only after partial pancreatectomy
Rats, Rabbits	Opposite effect—hypertrophy of islet cells and increased insulin content of gland
Man	Opposite effect? Aggravation of hypoglycemia in organic hyperinsulinism.[106] Islet cell hypertrophy found in acromegaly may be a response to this factor

No adequate explanation is available at present for the mechanism whereby the administration of crude anterior pituitary extract, purified growth hormone, ACTH, C_{11} and $C_{11,17}$ oxysteroids of the adrenal and thyroid extract produce the insufficiency of insulin which is expressed as diabetes. The relation of these factors to human diabetes will be discussed in the section on pathogenesis.

Dragstedt[46] described differences in the manifestations of diabetes between partially and totally depancreatized dogs. Partial pancreatectomy (95 per cent) results in "severe" diabetes requiring between 60 to 150 units of insulin daily and associated with a high blood cholesterol level, and a non-fatty liver. Excision of the remaining 5 per cent, total pancreatectomy, results in much less severe diabetes, the daily insulin requirement being 20 to 30 units, while an abnormally fatty liver develops in the presence of low blood cholesterol levels.

Alloxan, the ureide of mesoxalic acid, causes necrosis of the beta cells with subsequent atrophy and disappearance from the islets which then consist only of alpha cells.[1] This specific effect has not been found in human subjects except suggestively in 1 instance.[48] All other attempts to destroy the beta cells in patients with islet cell tumors failed to reveal any damage in these structures.[49,50,51] Many animals are entirely resistant to the diabetogenic effect of alloxan, including sheep, frogs and most birds.[5] In rats, protection against alloxan is possible by the preliminary administration of glutathione and cysteine,[53] BAL,[54] and sodium bisulfite.[55] A claim that transient diabetes and reduction of the insulin content of the pancreas to one third normal follows the intraperitoneal injection of uric acid into rabbits whose levels of blood glutathione were reduced by cysteine-methionine deficient diets[56,104] offered great promise but could not be confirmed.[57] The role of alloxan in the pathogenesis of human diabetes is an interesting but unproven conjecture.

Variations in the clinical manifestations of diabetes appear in the same animal when subjected *first* to alloxan, and then to pancreatectomy.[47] The alloxan diabetic dog presents more severe glycosuria with a higher insulin requirement than a depancreatized animal but is able to survive much longer than the latter without insulin and fails to develop ketosis or coma. When the alloxan-diabetic dog is subjected to pancreatectomy the character of the diabetes rapidly approximates that of the depancreatized animal. The glycosuria decreases but the animal is completely dependent upon constant insulin administration to keep it from dying of diabetic coma. This suggested the possibility that the *alpha* cells of the

islets undamaged by alloxan secrete a factor which *increases* the blood sugar level. Removal of the alpha cells has been offered as an explanation for the relatively mild but insulin sensitive diabetes characteristic of the totally depancreatized man.[47]

Alpha Cell Function.—Hyperglycemic Factor of Insulin.—The above *observations and the finding of transient hyperglycemia (five to ten minutes* duration) in animals and man upon intravenous injection of some commercial insulin preparations[48] suggested the possibility of a second hormone of the islets elaborated by the alpha cells and antagonistic in action to insulin.

The hyperglycemic factor isolated from insulin acts solely through increased liver glycogenolysis into glucose.[49] It is obtained from pancreas in roughly the same distribution as islet tissue and in normal amounts from the pancreas of alloxan-diabetic rats.[49] Its effect is apparent only when given intravenously, its subcutaneous administration being entirely ineffective. In addition to liver glycogenolysis it is presumed that some factor of the adrenal gland is necessary for the hyperglycemic effect.[50] Large doses of hyperglycemic factor proved ineffective in impairing the glucose tolerance of normal subjects or in aggravating existing diabetes in patients.[51] Its role in human diabetes is extremely questionable. This and the preceding discussions reflect the difficulty of applying data obtained from experimental diabetes in animals to the clinical syndrome in man.

PATHOGENESIS OF DIABETES MELLITUS IN MAN

The *insufficiency of insulin* which is fundamental to diabetes mellitus may be due to the following factors:

1. An absolute decrease in the available insulin (intrinsic severe pancreatic disease and total pancreatectomy).
2. An increase in the rate of insulin utilization (overfeeding, hyperthyroidism).
3. An increase in the rate of insulin destruction.
4. A decrease in the responsiveness of the enzyme systems affected by insulin (liver disease and the administration of ACTH, crude anterior pituitary extract, purified growth hormone).
5. The production of insulin antagonists or neutralizing agents.

Even though an individual may be predisposed to diabetes mellitus, the clinical syndrome may not appear until he has been exposed to a sufficiently intense or prolonged appropriate stress which may strain the efficiency of the regulatory mechanisms of metabolism to the point of failure.

The *predisposing* and *precipitating* factors include age, sex, multiple childbearing (especially of large babies), heredity, obesity, infections, trauma, endocrinopathies (hyperthyroidism, menopause, acromegaly and adrenal tumors), liver disease, arteriosclerosis and emotional conflict.

In the presence of an inherited or acquired limitation in the functional capacity of the pancreas, the increased requirements for insulin may become so stressful as to cause exhaustion and degeneration of the beta cells. In the presence of a normal pancreas, the insulin requirements may become so great as to exceed the secretory capacity of the pancreas and a relative

insufficiency may ensue. The clinical response to treatment will depend upon the nature of the factor inducing the increased insulin requirement as well as the functional reserve of the pancreas.

INCIDENCE OF DIABETES MELLITUS

During the next few decades the rate of increase in the number of diabetic individuals in the United States will be over 4 times that of the total population.[1] Over 1 per cent of the females and more than 2 per cent of the males in our population will eventually become diabetic.[1] The National Health Survey of 1935 to 1936[2] made by the U. S. Public Health Service provided an estimate of 660 000 as the number of diabetic patients in the country, with 35 000 *new* cases appearing annually. These figures must be revised upward in view of the Oxford (Mass.) survey, which revealed 3 undiscovered and unsuspected cases for every 4 known diabetic persons.[3] This case-finding study of a typical American town yielded an incidence of diabetes mellitus of 1.7 per cent. Sociologic factors such as the ever increasing proportion of persons living to an older age than formerly and the marked preponderance of females to males surviving to old age cannot account entirely for the increasing incidence of the disease. A diagnosis of diabetes was established in 1.6 per cent of registrants for Selective Service in the age group eighteen to forty five years.[4]

The British Ministry of Education survey revealed an incidence of diabetes in children of 1 in 180 000 under five years of age, 1 in 8000 for ages five to nine, and 1 in 3000 for ages ten to fifteen.[11] In this country the rate is 4 per 10 000 for all children under fifteen years of age, with an estimated total of more than 13 000 existing cases in this age group.[1] A review of the literature yielded 58 infants with diabetes under one year of age.[12] The youngest age of onset of diabetes ever recorded was obtained in 2 siblings in whom the disease was recognized at *three months* and at *nine days*, respectively.[33] Both are growing normally almost three years after the onset and receive a small dose of insulin daily.

PREDISPOSING FACTORS

Age and Sex.—According to the National Health Survey the incidence of diabetes rises slowly but steadily with age until the beginning of the fourth decade of life, after which a rapid progressive increase is noted with a peak in the seventh decade followed by a decline in the oldest age group, those in the eighth decade.[5] Joslin's[6] data reveal the age of maximum susceptibility to be fifty-one for males and fifty five for females. The considerable incidence in childhood, adolescence and early adult life as well as the declining susceptibility in the later decades indicate that diabetes is not typically a disease of old age. More than one-quarter acquired diabetes under fifty years of age and one-half between the ages fifty and sixty-four.[2]

No sex difference in prevalence of diabetes is noted in children, adolescents or young adults. The incidence among females begins to exceed that

of males after age of thirty Between forty five and sixty five years of age the preponderance of females rises to a level twice that of males The accelerated increase in diabetes among women with the approach of menopause is noteworthy

Marriage and Childbearing —The highest diabetic mortality occurs among married women (including widowed and divorced females)[7] This group presents a rate almost twice that of single women or married men (42 2 per 100 000 as compared to 23 and 22 5 respectively) However the diabetes death rate for married men is lower than that of single widowed or divorced men

The onus for the increased incidence of diabetes among married women has been attributed to the frequent association of obesity during and after pregnancy[8] According to a thorough study made in Glasgow[9] this concept is not valid for among women of comparable obesity diabetes appeared in direct relation to the size of the family The highest incidence coincided with the greatest number of children borne The possibility of hereditary diabetic tendencies was excluded by the observation that a family history of the disease was obtained with much less frequency in women who had borne 6 or more children They presented a familial background only one-third as frequently as women with 2 children or less These observers so carefully distinguished the role of obesity and heredity from the influence of multiple pregnancy among women that *childbearing per se* must be considered an important factor in the eventual development of diabetes The stress of repeated pregnancy plus the dynamic upheaval of the menopause may explain the predilection towards diabetes in women over forty years of age

Oversized Babies —In a brilliant investigation of the previous obstetrical histories of a large number of diabetic women Miller Hurwitz and Kuder[42] discovered that an increased stillbirth and neonatal mortality (characteristic of diabetes) is demonstrable fifteen to twenty years before the clinical symptoms and signs of diabetes are recognized Indeed during the five years immediately preceding the onset of diabetic symptoms the stillbirth and neonatal mortality is just as high as that after the disease has become established They also observed that unusually large infants with a birth weight of 5000 gm or more are born to women before they become diabetic with the same high frequency as that after diabetic symptoms have appeared Their findings indicate moreover that the presence of glycosuria in the last months of pregnancy in women whose carbohydrate metabolism is otherwise apparently normal is also associated with an increased fetal and neonatal mortality similar to that found in cases of diabetes

Subsequently Miller[43] noted an abnormally high incidence of the fetal visceral changes characteristic of infants of diabetic mothers in children born of prediabetic women Cardiac hypertrophy and extramedullary erythropoiesis in newborn infants as well as their excessive size and weight forecast the appearance of diabetes in the mother Kriss and Futcher[44] showed that as the birth weight of the baby rises the accuracy of the prediction of diabetes in the mother increases progressively and is greater than 60 per cent when the weight is more than 13 pounds

insufficiency may ensue The clinical response to treatment will depend upon the nature of the factor inducing the increased insulin requirement as well as the functional reserve of the pancreas

INCIDENCE OF DIABETES MELLITUS

During the next few decades the rate of increase in the number of diabetic individuals in the United States will be over 4 times that of the total population[1] Over 1 per cent of the females and more than 2 per cent of the males in our population will eventually become diabetic[1] The National Health Survey of 1935 to 1936[2] made by the U S Public Health Service provided an estimate of 660 000 as the number of diabetic patients in the country with 55 000 *new* cases appearing annually These figures must be revised upward in view of the Oxford (Mass) survey which revealed 3 undiscovered and unsuspected cases for every 4 known diabetic persons[3] This case-finding study of a typical American town yielded an incidence of diabetes mellitus of 1 7 per cent Sociologic factors, such as the ever increasing proportion of persons living to an older age than formerly and the marked preponderance of females to males surviving to old age, cannot account entirely for the increasing incidence of the disease A diagnosis of diabetes was established in 4 6 per cent of registrants for Selective Service in the age group eighteen to forty five years[4]

The British Ministry of Education survey revealed an incidence of diabetes in children of 1 in 180 000 under five years of age 1 in 8000 for ages five to nine and 1 in 3000 for ages ten to fifteen[11] In this country the rate is 4 per 10 000 for all children under fifteen years of age with an estimated total of more than 13 000 existing cases in this age group[1] A review of the literature yielded 58 infants with diabetes under one year of age[12] The youngest age of onset of diabetes ever recorded was obtained in 2 siblings in whom the disease was recognized at *three months* and at *nine days* respectively[33] Both are growing normally almost three years after the onset and receive a small dose of insulin daily

PREDISPOSING FACTORS

Age and Sex —According to the National Health Survey the incidence of diabetes rises slowly but steadily with age until the beginning of the fourth decade of life after which a rapid progressive increase is noted with a peak in the seventh decade followed by a decline in the oldest age group those in the eighth decade[5] Joslin s[6] data reveal the age of maximum susceptibility to be fifty-one for males and fifty-five for females The considerable incidence in childhood adolescence and early adult life as well as the *declining susceptibility in the later decades* indicate that diabetes is not typically a disease of old age More than one quarter acquired diabetes under fifty years of age and one *half between the ages fifty and sixty four*[2]

No sex difference in prevalence of diabetes is noted in children adolescents or young adults The incidence among females begins to exceed that

reducing both the severity of existing diabetes and the incidence of new cases is well known. Both obesity and diabetes are less frequent among *those engaged in farming or similar hard physical labor than among urban* sedentary workers.[6]

The incidence of diabetes is highest where 1) the average age is the oldest, 2) *women predominate*, 3) *obesity is most frequent*, 4) *medical* supervision is closest and 5) deaths are most accurately reported.[6]

Diet — The popular misconception that the incidence of diabetes parallels the consumption of sugar has not been substantiated. In fact, the opposite appears to be the case, since the lowest incidence of the disease is recorded in countries with the highest sugar consumption.[6] Himsworth[65] on the other hand noted a direct relationship of the diabetic mortality rate to the amount of fat in the diet. More important than the components of the diet is the total caloric intake, since *overfeeding* is such, both in the experimental animal and in man, is generally accepted as a significant precursor of diabetes. An interesting comment made by Joslin[6] states that "acute dietary excesses are rarely, *if ever*, associated with the advent of diabetes."

Heredity — It was Naunyn's[66] contention that with very rare exceptions the *underlying cause of diabetes is an inborn biologic inferiority*, primarily of the pancreatic reserve. An abnormally high incidence of diabetes is noted in (1) the similar twins of diabetics, (2) the offspring of two diabetic individuals, (3) the parents of diabetic children and (4) the siblings of the same sex of diabetic patients.[6]

If diabetes is encountered in one of a pair of twins, the incidence of the disorder in the other twin is dependent on the type of twinning. In fraternal twins this coincidence is noted on only 3.2 per cent, whereas in identical twins it is observed in 48.5 per cent.[6] After middle age this tendency for similar twins increases. Identical twin sisters seventy-four years of age living one thousand miles apart developed diabetes within the same month. Not only among twins but also among *siblings* with diabetes the age of onset tends to be about the same.[67] However, I have seen 2 families where diabetes appeared in pseudoepidemic form, striking all 3 children within the same year although their ages differed by as much as ten years! In 1 instance no familial history of diabetes could be discovered even during the years since the onset. The other family gave a history of diabetes in maternal and paternal cousins.

Among diabetic children the incidence of the disease in parents and grandparents is at least twice that of a random sample.[6] The phenomenon of *anticipation* is characteristic of diabetes in that it tends to appear earliest in the third generation, later in the second generation and latest in the first generation.[68] In other words, a diabetic child may give a negative familial history of the disease at the time of onset, but often within the succeeding years first a parent and later a grandparent may develop it, the child "anticipating" it for the rest of the family.

Colwell[69] by an ingenious calculation using the average annual increment of insulin requirement carries the slope of such curves back into the prediabetic period of early infancy. He concludes that diabetes is inherited

The following case history illustrates the point that some pathogenetic factor is operative *long* before diabetes becomes manifest clinically, expressing itself by gigantism in the responsive organism of the fetus.

Illustrative Case

A non-obese young woman whose *mother*, maternal *grandmother* and *aunt* had been diabetic had a *stillborn* child (birthweight not recorded) at the age of twenty-two years. Three years later, at the age of twenty-five years, she gave birth to a normal living infant weighing 10 pounds. Two years later, when twenty-seven years old, *glycosuria* appeared in the fifth month of her third pregnancy, but was dismissed casually because of a normal fasting blood sugar level. The glycosuria was unaccompanied by symptoms and disappeared immediately postpartum. This time she was delivered of an 11½ pound living normal infant. She remained well for a period of four years thereafter, when at the age of thirty-one years thirst, polyuria and pruritus vulvae were noted. A fasting blood sugar level of 245 mg. per cent with glycosuria of 5 per cent was obtained. Insulin therapy, begun at that time, has continued to date. Both children appear normal at present.

Comment.—The marked familial history of diabetes, the stillbirth and the subsequent delivery of 2 oversized infants (over 5000 grams) foretold eventual diabetes. No evaluation of the glycosuria during the last pregnancy is possible in the absence of further data. Of interest is the interval of nine years between the first portent and the clinical onset of symptoms.

Race.—Many of the purported racial and geographic variations in incidence of diabetes lack validity because the following factors have not been considered:

1. *Degree of urbanization*, which makes for more available medical care, more frequent diagnosis and better mortality records. Diabetes, reportedly infrequent among Negroes in the South, appears to be as frequent among Northern Negroes as in the white urban population.[5] For the country as a whole, the death rate from diabetes among the white and Negro urban population is more than 50 per cent above the rural rate.[5] The higher rates found among Jewish,[6] Irish[4] and Italian[4] people reflect the tendency for these groups to congregate in the cities. When Joslin[9] personally investigated the reported low incidence of diabetes in the state of Arizona, he was able to ferret out sufficient numbers of undiagnosed cases to bring the rate up to that of Rhode Island.

2. *Longevity* makes for an increased incidence of diabetes, and this country with so many of its people surviving to older ages is credited with the highest rate in the world.[5] The contrary obtains in eastern and southern Europe, Latin America and the Far East.

3. *Undernutrition and semistarvation* are associated with a lowered incidence of diabetes in the latter countries. The rate corresponds to the level of nutrition, which in turn reflects the level of *per capita* income.[6] Snapper[10] found diabetes to be quite frequent among the average Chinese, but because of the low caloric, low animal fat diet the condition appeared in mild form (never requiring more than 20 units of insulin daily) and uncomplicated by coma or gangrene. Severe diabetes with a tendency to ketosis and arteriosclerotic complications was characteristic of the overfed Chinese merchant class. The influence of food restriction during wartime in

When appetite is so affected that an excessive food intake results, an increased need for insulin occurs to satisfy the necessary increase in metabolic disposal of the foodstuffs via storage, oxidation or conversion to fat.[73] The normal human pancreas can compensate quite adequately for this increased demand by producing more insulin. However, when this compensatory overactivity reaches a maximum and begins to lag behind the rate of insulin need and utilization, a *relative insufficiency of insulin* (diabetes) ensues. Decreasing the food intake and thereby decreasing the insulin need to a point equal to or below the available insulin reserve will abolish the relative insufficiency. This is the explanation for Newburgh and Conn's[74] excellent results in the treatment of the obese mild diabetic by weight reduction. In this sense too every obese individual is a "*compensated diabetic*."[75]

Disease of the Liver and Biliary Tract ("Hepatic Diabetes").—The role of the liver in carbohydrate metabolism first suggested by Claude Bernard[76] was confirmed by the work of Mann and Magath.[77] Soskin in conjunction with the latter and others[78] established the principle of the homeostatic mechanism of the liver in blood sugar regulation. However, the diminished carbohydrate tolerance associated with parenchymatous liver damage cannot properly be termed diabetes or even "hepatic diabetes." The fundamental problem here is *not* insulin insufficiency with all its attendant metabolic disturbances, but rather impaired glycogen storage and glycogenolysis. The delayed glycogenesis following carbohydrate administration leads to abnormal hyperglycemia and glycosuria which responds to carbohydrate therapy and *not* to insulin.[79] These patients tend to develop spontaneous hypoglycemia on fasting (*see* section on hepatogenic hypoglycemia, p. 1046) due to inadequate liver glycogen reserve and decreased glycogenolysis. Sensitivity to insulin is therefore noted when the usual diabetic regimen of restricted carbohydrate intake and insulin administration is employed mistakenly. The so-called diabetes disappears when the underlying organic disease (hepatitis[80] and cholangiolitis[81]) is treated successfully. The following case history illustrates the characteristics of non-diabetic hepatogenic post prandial hyperglycemia.

Illustrative Case

A fifty two year old woman suffering from generalized lymphosarcomatosis received intense radiotherapy to the upper abdomen. Moderate jaundice developed with laboratory evidences of both biliary obstruction and parenchymal liver damage. During this time thirst and polyuria were noted and glycosuria found. Despite restriction of dietary carbohydrate to 150 grams and the daily administration of 20 units of protamine zinc insulin daily, glycosuria continued unabated with the additional disturbance of severe hypoglycemia before meals and during sleep. This program was discontinued as the diagnosis became evident. An oral glucose tolerance test (100 grams) revealed the following:

Time in hours	*Fasting*	½	*1*	*2*	*3*	*4*	*5*
Blood Sugar in *mg. per cent*	72	105	264	202	147	105	56

After the disappearance of jaundice and other symptoms, the glucose tolerance test three months later had returned to normal.

beginning its course at birth and progressing through an unrecognized phase approximately equal to the period of clinical recognition

A familial history of diabetes is noted in 25[8] to 30[8] per cent of patients. Investigation for latent familial diabetes by means of glucose tolerance tests have proven futile. In fact, it is scarcely ever possible with this method to recognize premorbidity in a patient liable to develop diabetes.[9]

Illustrative Case

An extremely obese ten year old girl whose mother, paternal grandparents *and several aunts and uncles on both sides were diabetic* was subjected to glucose tolerance tests annually in the expectancy of finding an abnormality preclinically. However, these were normal repeatedly over a period of four years. Six *months after* the last normal test she developed polyuria and polydipsia. A fasting blood sugar of 300 mg per cent and 6.6 per cent glycosuria were obtained. A comparison of the glucose tolerance tests before and after the onset of diabetes using 100 grams of glucose follows

	Time in hours	*Fasting*	½	*1*	*2*	*3*
March 1941	Blood Sugar	120	192	204	146	118
	in					
Sept 1941	mg per cent	300	340	434	492	789

The generally accepted belief that the hereditary pattern of diabetes is that of a *Mendelian recessive character*[6] has been most precisely confirmed by Hanhart.[9] The latter made his observations in a unique situation using the inhabitants of a small Swiss village isolated from the world more or less for many centuries. With well-documented family histories, long lived ancestry and large families, an ideal opportunity was provided for the disease to display itself fully. Further confirmation of the hereditary pattern of diabetes was obtained by the observed association of an increased incidence of taste blindness, another recessive Mendelian character, with diabetes.[71]

The factor of heredity even appears to be extremely important in diabetes associated with hyperthyroidism and acromegaly. A familial history of diabetes occurred as commonly among diabetics with hyperthyroidism as among those *without* this complication.[8] In patients with acromegaly and diabetes a positive familial history of the latter was noted in 21 per *cent of cases with both diseases and in only 2 per cent of cases with acromegaly* alone.[7] Unquestionably an inherited inadequacy of insulin reserve is required before the other predisposing factors for diabetes become effective.

Obesity.—While heredity is the most important *predisposing* factor in the pathogenesis of diabetes, *obesity* is equally significant as the most common *precipitating* factor. Notwithstanding the fact that only 5 per cent of the total obese population develop diabetes and that only 2 per cent of diabetic children present a history of previous obesity, *77 per cent* of all patients with diabetes are *above* maximum normal weight before the onset of the disease.[6] The latter represent that minority of the total obese population who have hereditary predisposition to diabetes. An impaired glucose tolerance in obese persons has been found only in those with a familial history of diabetes.[6]

ance of diabetes followed the removal of an adrenal cortical tumor.[89] Glucose tolerance tests remained normal thereafter. Similar results have been noted in cases with pheochromocytoma.[90, 91]

ACTH administration produces hyperglycemic plateau glucose tolerance curves in normal human subjects according to Conn.[92] Others do not find any measurable effect upon glucose tolerance, only a slight resistance to insulin.[93] *Compound E* administration to normal human subjects produces only *mild transient* impairment of the glucose tolerance curves.[94, 95] That the resistance to insulin characteristic of "steroid diabetes" is partly a peripheral phenomenon and not attributable only to a decreased insulin production by the pancreas is indicated by its occurrence when ACTH is administered to the alloxan-diabetic rat.[96]

The following case was observed recently.

Illustrative Case

A fifty-one year old man was admitted November 2, 1949 for typical lupus erythematosus. On January 26, 1950 the daily administration of 100 to 150 mg. of *Cortisone* was begun for a period of sixteen days. Fasting blood sugar levels were normal, 80 to 87 mg. per cent throughout this period and no glycosuria was observed. On February 11, 1950 *ACTH* therapy was substituted for Cortisone beginning with 75 mg. daily with gradually reducing dosage. Four days later, February 15, 1950, polyuria, glycosuria and hyperglycemia were noted for the first time, the fasting blood sugar level being 230 mg. per cent. For the past three months glycosuria and hyperglycemia have continued even during 2 periods of cessation of ACTH therapy lasting two days (severe recurrence of the systemic disease, lupus erythematosus, precluded cessation of ACTH for a longer period). Variable glycosuria up to 90 grams daily was noted, requiring between 60 to 100 units of insulin daily to obtain decreased glycosuria. No correlation could be obtained between the amount of insulin required and the alterations of ACTH dosage. The appearance of the diabetic syndrome prompted an investigation of the familial history of the disease. The patient's *father*, *sister* and 2 paternal *cousins* were revealed to have had diabetes!

Comment.—The marked *familial history* of diabetes and the *age* of the patient account for his unusual susceptibility and predisposition towards diabetes following ACTH administration. The effect of Cortisone cannot be discounted entirely, however, since the period of its administration overlapped into the beginning of ACTH therapy.

Menopause and estrogen deficiency, suspected as possible precipitating factors because of the age and sex distribution of diabetes and the occasional aggravation of existing diabetes by the menses, have not been demonstrated as playing such a role unequivocally.

In summarizing the influence of endocrine factors in the precipitation of diabetes it appears that a predisposing inadequacy of insulin reserve (limited to heredity according to our present knowledge) is a prerequisite for their effect.

Trauma and Infections.—The precipitation of diabetes by infection or trauma can be attributed to the nonspecific reaction of "stress" ("alarm reaction")[97] evoking an ACTH response plus the marked protein catabolism characteristic of trauma[98] which is independent from the adrenal anterior pituitary factor.[99] Infection and trauma causes an increase in the insulin

Endocrine Factors — The enormous activity and productivity of recent research into the functions and *interrelationships of the various endocrine* glands have given little to the elucidation of the actual role these factors play in the pathogenesis of human diabetes These investigations have proven more fruitful in expanding our knowledge of the physiology of diabetes, the action of insulin, and the factors aggravating or ameliorating pre-existing diabetes Since the influence of the various endocrine glands upon carbohydrate metabolism is presented in detail in other chapters, this discussion will be limited to their possible effects in precipitating diabetes

Thyroid hyperfunction causes an increase in 1) intestinal absorption of carbohydrate, 2) glycogenolysis and 3) the rate of utilization of carbohydrate, fat and protein Experimentally the administration of thyroid extract induces diabetes only after partial pancreatectomy [82] Clinically, hyperthyroidism is the most commonly encountered endocrine disorder associated with diabetes (3 per cent[6]) These patients, however, present evidence of diabetic susceptibility in their familial history of the disease, the incidence of which is identical to that of diabetic patients *without* hyperthyroidism [8]

Interior pituitary hyperfunction is considered by Lukens[83] to be a possible factor in the etiology of *juvenile* diabetes because of the greater than average height and growth these children present at the onset of the disease and because of the specific diabetogenic effect of purified growth hormone in animals [105] Although the incidence of diabetes in acromegaly is 10 times that of the general population so is a familial history of diabetes found to be increased tenfold in patients with both diseases as compared to those with acromegaly alone [72] Prolonged exposure to the diabetogenic *process is apparently necessary as indicated by the long interval of nine* years on the average between the onset of acromegaly and the appearance of diabetes [72]

Adrenal cortical hyperactivity has *not* been demonstrated in diabetes mellitus apart from those instances associated with Cushing s syndrome The urinary excretion of 17 ketosteroids and glycogenic corticoids in diabetes is normal[84] or even reduced [85 86] Although the association of Addison s disease with diabetes produces an amelioration of the latter the Mayo Clinic recently reported such a combination in which *no* significant reduction in severity *of the diabetes occurred* [87] *In this patient the urinary* output of corticosteroids was normal while that of 17 ketosteroids was reduced

The frequent occurrence of diabetes in Cushing s syndrome adrenal cortical tumors and pheochromocytoma is discussed in the chapters concerned with these conditions Of interest here are the absence of significant pancreatic abnormalities at necropsy [88] and the dramatic cure of the diabetes following removal of the tumor Unlike the purported effect of prolonged hyperglycemia in producing islet cell lesions and permanent diabetes in cats, [3] *no such residual disturbance has been found* in these patients following successful operation One patient required as much as 145 units of insulin daily for a period of three years and despite the duration of almost constant glycosuria and hyperglycemia prompt disappear

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requirement of the totally depancreatized animal Recovery from the infection or trauma may be followed by remission of the diabetic syndrome depending again upon the inherent tendency of the patient towards the disease

Emotional Factors — The rigidly mathematical philosophy of diabetic treatment which prevailed until recently did not allow for any consideration of the human being attached to the disease In the style of a cooking recipe so much insulin took care of so much carbohydrate and a neat adjustment by a little calculation of just these 2 variables supposedly provided a simple and ready solution of the therapeutic problem In the course of time it became evident that the equalization of just 2 factors insulin *versus* food was an oversimplification In addition to such recognized physical influences as exercise the general state of health *etc* emotional conflicts have come to be accepted as important in the stability and course of existing diabetes The role of emotional factors in the precipitation of diabetic ketosis has been established by several recent observations[102 103] The aggravation of the diabetes which follows emotional excitation is due not only to increased hepatic glycogenolysis by epinephrine but more significantly to the chain reaction set up by epinephrine on adrenal cortical function via the tropic hormones of the anterior pituitary It is conceivable that prolonged repeated excitation may prove so great a stress to persons with relatively inadequate insulin reserve that diabetes may ensue Although Woodyatt[100] has gone further in proposing that emotional disturbances are notoriously capable of provoking the onset of diabetes his contemporary Joslin dismisses the entire subject of psychogenic influences at any phase of diabetes[6]

The fact that severe emotional trauma such as exposure to combat only rarely produces diabetes is cited as an argument against this concept However the *intensity* of the psychologic trauma is not as essential as is the *soil* upon which the trauma impinges[101] a point previously made with regard to such pathogenetic factors as obesity hyperthyroidism *etc* The psychodynamics of diabetes mellitus are just beginning to be investigated and we all await the integration of the physiologic and psychologic mechanisms of the disease

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Chapter 31

THE PHYSIOLOGIC AND METABOLIC DERANGEMENTS IN DIABETES MELLITUS

By Henry Dolger M D

Introduction.—The physiologic disturbances which characterize diabetes mellitus are now recognized as encompassing the total metabolism in contrast to the limited approach of earlier years The rapid interconversion of carbohydrate protein and fat obtained from food the associated alterations in electrolyte vitamin and fluid balance the role of the liver and endocrine system in metabolic regulation the capacity of fatty acids and the ketone bodies to replace carbohydrate as a source of energy for muscle tissue and the ability of the untreated diabetic organism to utilize glucose indicate the growing complexity of physiologic mechanisms which formerly seemed so simple The *venerable* concepts of the specificity of the respiratory quotient the fixed urinary glucose-nitrogen ratio in diabetes the antiketogenic ketogenic ratio of the diet fat burning in the flame of carbohydrate and the beta oxidation of fatty acids have been modified drastically

The Energy Derived from the Metabolism of Carbohydrate Protein and Fat.—Apart from the direct need for certain essential amino and fatty acids the primary function of the metabolic degradation of foodstuffs is to supply the enormous amounts of energy needed for such energy requiring reactions as the maintenance of body temperature the performance of mechanical work by muscle contraction the functions of nerve tissue and secretory organs and the synthesis of newly formed aggregates of carbohydrate protein and fat in the constant turnover of the metabolic pool

The energy yielding reactions do not liberate it in a single large burst *but in a series of steps marked by specificity of interaction each component* reacting readily only with that immediately preceding or following it Very little of the energy derived immediately from the breakdown of glucose is dissipated as heat most of it being converted into chemical energy by the formation of new compounds capable of accepting energy and transforming it into useful work This process permits the energy released by one reaction to be transferred to and used by another reaction occurring simultaneously without its being lost from the system The potential energy *of such compounds may be derived either from the presence of an* unstable group of atoms or by the incorporation of energy bearing phosphate compounds Although the formula for lactic acid and triose is identical ($C_3H_6O_3$) the latter has much higher potential energy because of its unstable groups

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bonds result from each molecule of glucose degraded to pyruvate or lactate. Furthermore the metabolic intermediates, the alpha and beta ketoacids derived from *protein* and *fat*, on entering the glycolytic cycle can also serve as fuel for muscle work by restoring ATP.[2]

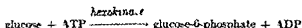
The *coupling* between *phosphorylation* and *oxidation* first demonstrated by Lundsgaard indicates that not only can the potential energy of compounds be released under anaerobic conditions, but also that phosphates take part in the substrate oxidation. Of clinical interest is the suggestion that the phosphorylating mechanism may be the first to be lost in shock or anoxia.[3] In a study of traumatic shock in rats, Haist[4] found no appreciable reduction in ATP or phosphocreatine in concentration or turnover *except in the damaged limb*. *However, marked reduction of liver and* muscle glycogen was found (including that of unimpaired muscle) in addition to hyperglycemia and impaired glucose tolerance. Kaplan and Greenberg[5] on the other hand, observed a decreased ATP of the liver after starvation or high fat rations, with an increase after insulin administration. The vital need of brain tissue for high-energy stores is indicated by the stability of its ATP and ADP content after fatal hemorrhage while that of muscle is reduced and completely depleted in liver and kidney.

In heart muscle preparations from alloxan diabetic rats Goranson,[6] although observing a normal oxygen uptake without change after insulin administration, did note a decreased aerobic phosphorylation of creatine which was restored to normal by insulin. He concluded that insulin participates directly in reactions of the tricarboxylic acid cycle leading to a more *efficient coupling* between phosphorylation and oxidation.

INTERMEDIARY METABOLISM

A discussion of the intermediary metabolism of glucose must include its conversion to glycogen both in liver and muscle (*glycogenesis*), its release from this form of storage (*glycogenolysis*) and the steps involved in its breakdown to carbon dioxide and water (*glycolysis*). In the latter 3-carbon chains are formed. These play an important role in the interconversion of carbohydrate, protein, and fat.

Glucose, the main transport form of carbohydrate, is too readily diffusible for its fixed intracellular requirement. Therefore all living cells contain an irreversible mechanism whereby the freely diffusing glucose molecule is converted to a poorly diffusible phosphate, insuring its intracellular retention. This, the *hexokinase reaction*, has been the subject of great great interest and controversy. The ubiquitous reaction is as follows:



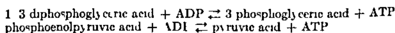
$$\text{glucose} + \text{ATP} \xrightarrow{\textit{hexokinase}} \text{glucose-6-phosphate} + \text{ADP}$$

Hexokinase Reaction.—Cori and his associates[5,9] claimed that muscle and liver hexokinase reactions are inhibited by anterior pituitary extract, an inhibition which is further potentiated by adrenal cortical extract. No such effect, however, was observed in the cells of the central nervous system, *renal tubule* or *intestinal mucosa*. Insulin had no effect whatso-

Phosphorylation, the incorporation of energy-bearing phosphate bonds derived from the adenosine triphosphate (ATP) system is accomplished by the action of an enzyme, *phosphorylase*[29] This process is essential for the entry of glucose, fructose and galactose into the metabolic cycle[30] and more recently the same mechanism has been demonstrated in pyruvate and fatty acid oxidation[31] Intestinal absorption of the hexoses renal tubular reabsorption of glucose, and the synthesis of acetylcholine for transmission of the nerve impulse are all dependent upon phosphorylation in order to perform their specific functions

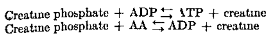
Lipmann[1] originated the concept of classifying organic phosphate compounds according to the potential energy of the phosphate bond The most common are the simple ester phosphates (hexoses and trioses), and include for example glucose 1 phosphate, and glucose-6-phosphate The hydrolysis of such relatively stable compounds is readily reversible and yields a *low energy* potential (3000 calories) *High energy phosphate bonds* yield 10 000 calories on hydrolysis which proceeds irreversibly and completely This energy-rich group comprises such phosphate bonds as P O P (adenosine triphosphate ATP) N P (phosphocreatine) and enol P (phosphopyruvic acid) The continual turnover of phosphorus from low energy esters to high-energy forms and vice versa insures the maintenance of a reservoir of energy readily available for the processes of muscle contraction anabolic synthesis, *etc*

The *ATP system* is a unique mechanism and the common link between energy requiring reactions and energy yielding ones The loss of its 2 high-energy phosphate bonds transforms ATP first to ADP (adenosine diphosphate) and then to AA (adenosine monophosphate or adenylic acid), respectively Since the ATP content of the cell is small compared to the amount of material to be phosphorylated ADP and AA must be constantly reconverted to ATP so that the latter may serve as a continuous phosphate donor Examples of two means of rephosphorylation to ATP occurring in the breakdown of glucose follow


1 3 diphosphoglyceric acid + ADP ⇄ 3 phosphoglyceric acid + ATP
phosphoenolpyruvic acid + ADP ⇄ pyruvic acid + ATP

The latter reaction is irreversible under anaerobic conditions but is reversible in the presence of simultaneous oxidations

Muscular contraction represents the release of kinetic energy a drop in potential energy and the loss of inorganic phosphate at zero level of energy The preparatory *extension* of the muscle fibril is accompanied by an increase in potential energy derived from the introduction of high-energy phosphate The latter is obtained from ATP by the action of *myosin* which consists of adenosine triphosph*atase*[32] The small amount of ATP is inadequate in itself for continued muscle work but a secondary larger reservoir of high energy phosphate is contained within the *creatine phosphate stores* of muscle tissue


Creatine phosphate + ADP ⇆ ATP + creatine
Creatine phosphate + AA ⇆ ADP + creatine

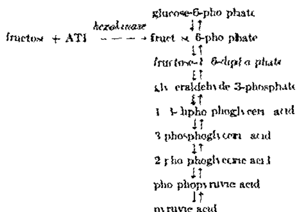
The intracellular breakdown of *glucose* insures continued replenishment of high-energy phosphate for the creatine phosphate reservoir, since 2 such

retention in the liver. Similarly, any factor which inhibits the formation of glucose-6-phosphate from glucose *via* hexokinase would tend to favor glycogenolysis. The relative *velocities* of the hexokinase and glucose-6-phosphatase reactions in the liver distinguish the normal from the diabetic organism. In the *diabetic* the velocity of the phosphatase reaction must surpass that of the hexokinase reaction, even if the latter is unchanged.[13] This instability of liver glycogen in the diabetic is well known both clinically and experimentally. *In contrast, the glycogen of muscle is much less labile because this specific phosphatase is absent.* As a consequence, therefore, muscle glycogen cannot contribute glucose directly to the circulation even for the critical need arising during hypoglycemia. In muscle phosphorylation continues further to yield a hexose *di*phosphate which in turn rapidly breaks down to either pyruvic or lactic acid.

An attempt to implicate *increased liver phosphatase activity* as the defect in diabetes was made by Drabkin and Marsh.[14] They found an increase in both acid and alkaline liver phosphatases in alloxan diabetic rats which *responded to insulin while others*[15] *found an increase in serum alkaline* phosphatase in similar animals. Mirsky,[16] however, who isolated the specific glucose-6-phosphatase in the liver, proved it to be entirely *distinct* from the so-called acid and alkaline phosphatases. At present none of the enzyme systems involved in the glucose ⇌ glycogen cycle of the liver have proven to be affected directly by insulin.

Glycolytic Cycle.—Glucose-6-phosphate in the liver has been shown to have a choice of 3 pathways, ending as glucose or glycogen, or via the cycle of glycolysis as pyruvic acid. In muscle it may end as glycogen or pyruvic (or lactic) acid, *there being no phosphatase to form glucose as such.* The degradation to the 3-carbon stage is the same in both tissues and is initiated *by the transformation to fructose-6-phosphate.* This is also the point of entry for exogenous fructose into the carbohydrate metabolic cycle.

Schematically, the series of reversible reactions is as follows:

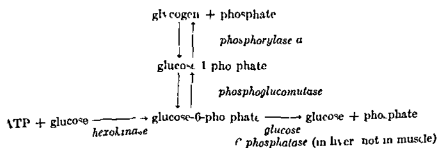


The above biologic oxidations and molecular rearrangements are effected by an intricate series of enzyme systems described in more detail in texts on biochemistry or physiology. Of clinical interest is the fact that these

ever on hexokinase itself since it did not enhance the activity of the reaction. The sole *function* of insulin, according to these observers, is to release hexokinase from the inhibitory influence of anterior pituitary and adrenal cortical extracts. These results, obtained both *in vitro* and *in vivo*, were accepted as supposedly explaining the mechanism of insulin action and the *defect in diabetes mellitus*. Apparently blocked at its introduction into the metabolic cycle, glucose would continue to arise from its normal sources, depleting the liver glycogen stores and increasing its concentration in the blood to the point of glycosuria. Demand upon the secondary sources of energy, gluconeogenesis from protein and excessive ketone body production from fatty acid, would lead to the protein loss and ketosis associated with diabetes.

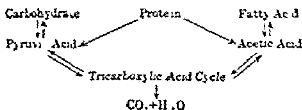
The first doubt cast upon this theory arose from the well known observation that hypophysectomized and adrenalectomized animals are unusually *sensitive* to insulin. This could not be explained if insulin were to have *no* effect in the absence of these two glands. Broh-Kahn and Mirsky[10] then found that 1) splenic extracts actively inhibited hexokinase activity *in vitro*, 2) the hexokinase activity of muscle from alloxan diabetic rats was normal, and 3) the addition of insulin failed to increase the activity of either normal or diabetic muscle extracts. Stadie and Haugaard[11] also failed to confirm Cori's observations, finding no alteration of hexokinase reaction in muscle or kidney extracts from diabetic rats when compared to normal controls. Further proof of a lack of hexokinase inhibition in alloxan diabetes was offered by Chaikoff and his associates[16] who found the rate of conversion of isotope-labeled glucose to CO_2 (measured in the expired air) to be no different in the diabetic compared to the normal rat. The entry of glucose into the cells and its utilization in the untreated depancreatized dog has been demonstrated following the injection of large amounts of glucose without insulin.[17] Although no evidence exists that insulin affects the hexokinase system *per se*, it must exert its physiologic action somewhere in the glucose ⇄ glycogen cycle.

Glucose Glycogen Cycle.—The *first* intermediate formed in the conversion of glucose to glycogen and the *last* metabolite produced in the reconversion of glycogen to glucose is glucose-6-phosphate. The latter therefore serves as the fulcrum for both the glycogenolytic and glycogenic mechanisms, as follows:



Since the two uppermost reactions are reversible, any factor which inhibits the breakdown of glucose-6-phosphate would tend to favor glycogen

metabolism. Finally, liver glycogen may be resynthesized by condensation of pyruvic acid and CO_2 to phosphopyruvic acid *via* oxaloacetic acid and inorganic phosphate. The following schematic presentation illustrates the interrelationship of carbohydrate, fat and protein metabolism.



In diabetes the blood pyruvic and lactic acid levels are normal both at rest and with exercise. However, the administration of glucose fails to produce the normal rise in pyruvic acid. No insulin effect upon pyruvate utilization by human and rat muscle could be demonstrated. Mention has been made on Gorinson's observation as to the possible influence of insulin on the tricarboxylic acid cycle. Therapeutic attempts to overcome tissue anoxia in diabetic patients suffering from severe arteriosclerotic complications using some oxidative components of the citric acid cycle, such as succinic acid and cytochrome C, have proven useless.

The *interconversion of succinate to pyruvate and citrate appears to be* normal in the diabetic subject, even in the absence of insulin. Apparently the intermediary reactions of these compounds are not dependent upon insulin.

THE INTERCONVERSION OF CARBOHYDRATE, FAT AND PROTEIN

The concept of a common metabolic pathway for the three types of foodstuffs evolved by Schoenheimer and Rittenberg[25] has replaced that of strict compartmentation of such mechanisms for each nutrient substance. Integration of the fragments derived from any kind of food into the tricarboxylic acid cycle provides an explanation for many physiologic phenomena.

Storage.—It is estimated that the entire carbohydrate stores of the body including all muscle and liver glycogen (about 300 grams) would be depleted by the daily caloric needs in but a fraction of one day were it not for the ingestion of carbohydrate and the conversion of other food materials into carbohydrate.[26]

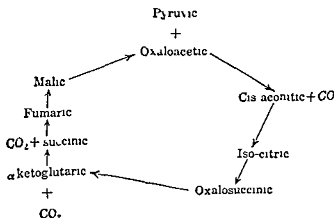
Fat provides the great energy reserve of the body, being deposited in a practically anhydrous state and yielding the highest caloric values in proportion to weight. A gram of carbohydrate or protein provides 4 calories but requires 3 grams of water for storage. A gram of fat, yielding 9 calories, is stored in almost pure form and therefore is 9 times more efficient as a source of energy per unit of weight for the organism.[27]

The inanimate plant abounds in carbohydrate stores, fat being rather scanty. The extreme motility of the animal is predicated on the concen

oxidative enzyme systems contain nicotinamide (co-enzymes I and II), riboflavin (flavoproteins) iron porphyrin (cytochromes), and the adenylic acid system

Lactic Acid Cycle — The reaction pyruvic acid ⇌ lactic acid is not an obligatory intermediate of carbohydrate metabolism but represents a blind alley, an emergency mechanism during muscle anoxia. With adequate oxygen supply to the muscle glycogen breakdown proceeds beyond pyruvic acid in a manner to be described, while none is reduced to lactic acid. At the beginning of severe muscular effort before the circulatory adjustment becomes adequate pyruvic acid is reduced to lactic acid thereby maintaining co-enzyme I in oxidized form. The increased lactic acid serves in the synthesis of glycogen when it reaches the liver, or is re-oxidized to pyruvic acid when exertion is over. Ten per cent of isotope-labeled lactate has been found to be changed to ketone bodies without first becoming fat.[100]

Pyruvic Acid Oxidation — Pyruvic acid is an extremely reactive substance and some 17 different metabolic pathways have been observed in living cells.[18] It represents the means for interconversion of carbohydrate fat and protein the assimilation of CO_2 and the source of acetylation. *Its complete oxidation to CO_2 and water requires the cyclophorase system*[19] which is widely distributed in all animal tissues and operates *via* the oxidative enzyme systems already described plus that containing thiamin (cocarboxylase) and the group of tissue metabolites comprising the *Krebs tricarboxylic acid cycle*.[20] The first step in the latter is the condensation of pyruvic acid with oxaloacetic acid forming *cis* aconitic acid CO_2 and water. By the successive oxidation to succinic acid all 3 carbon atoms of pyruvic acid are converted to CO_2 and 2 of the H atoms to water. At this point the *dicarboxylic acid cycle* of Szent Györgyi[21] contrives to regenerate oxaloacetic acid from succinic acid. Thus, the conserved oxaloacetic acid returns to the cycle by reacting with another molecule of pyruvic acid as follows



Pyruvic oxaloacetic and α ketoglutaric acids may be reversibly converted to amino acids. Acetoacetic acid will form citric acid and some strains of rat will convert pyruvic acid to acetic acid[3] linking fat and carbohydrate

ponent of oxidative metabolism and therefore inadequate for the tremendous energy requirement of glycogen synthesis.[1] Therefore the glycogen stores of the diabetic can be increased by fatty acid only with concomitant participation of glucose in the oxidative cycle.

Gluconeogenesis from Protein.—Dietary protein is the major non-carbohydrate source of glucose and glycogen. *Deamination* of amino acids in the liver leads chiefly to the production of keto acids which may then enter the tricarboxylic acid cycle. Insulin has no direct influence in the deamination of natural amino acids.[33] Since glycogen can be formed in varying amounts from nearly *all* the primary amino-acids[43] (lysine, leucine and tryptophane being the only exceptions) the old classification of proteins as *ketogenic or glycogenic* can be discarded. The concept of a fixed *derivation* of 48 to 58 per cent of *protein as eventual carbohydrate* must likewise be invalid.

Inability to reconcile the different *G:N ratios* of the phlorizinized *versus* the depancreatized animal, and the wide variations obtained in human diabetes limit the reliability of this factor as an index of the protein origin of urinary glucose. Crandall and Lipscomb[34] claim that, in view of the demonstrated utilization of glucose by brain and gastro-intestinal tract in diabetes, and the evidence that appreciable glucose is retained, the ratio of glucose to nitrogen in the urine appears to be meaningless. Using the direct technic of hepatic vein catheterization in *patients* with diabetic ketosis Bondy and his associates[35] found similar inconsistencies with variations in glucose produced from protein ranging from 8 to 42 per cent of the total hepatic glucose output.

Protein does not assume the role of carbohydrate synthesis until the liver glycogen is *greatly* reduced. The initial sharp decrease in hepatic glycogen which occurs on fasting is followed by an *increase* as fasting continues for several days, due to the continued gluconeogenesis from protein.[37]

Protein Catabolism in Diabetes.—As gluconeogenesis from protein increases in the untreated diabetic patient *in ketosis* a marked *negative nitrogen balance* develops.[36] *Insulin* administration in the presence of available carbohydrate induces reversal to a *normal* protein metabolism[38, 61] so rapidly that inhibition of hepatic urea formation (the index of amino acid deamination) parallels and may even precede its carbohydrate effects.[39] Whereas insulin inhibits gluconeogenesis from protein, the anterior pituitary and adrenal cortex enhance it.

Protamine zinc insulin, because of its continuous effect, prevents gluconeogenesis from protein in the diabetic despite fairly marked glycosuria. Wilder[61] first noted the clinical superiority of long acting insulin over regular insulin in this respect. He pointed out the frequent occurrence of acetonuria and a negative nitrogen balance in severe diabetes during sleep and in the prolonged intervals between meals even in the absence of glycosuria when regular, unmodified insulin was used. Protamine zinc insulin being constantly available at all times during the 24-hour period *prevented* this periodic ketonuria and azoturia, even in the presence of *glycosuria*. The intermittent catabolism of protein and fat characteristic of the early insulin era was manifested clinically by inadequate growth and development (dwarfism) and enlarged fatty livers, especially in diabetic children.[58]

trated storage of large amounts of fat and relatively little carbohydrate[38] In contrast to the adult animal, the fetus resembles the plant in being a glycogen storing organism suggesting to Stetten[33] that liver glycogen is a vestigial biochemical cul-de-sac with a limited reserve of both energy and glucose The dependency of *normal and diabetic children* and *diabetic adults* upon the labile liver glycogen reserve accounts for their marked susceptibility to ketosis when deprived of carbohydrate[39] The tendency towards fasting ketosis and depletion of liver glycogen in animals likewise *decreases* with age[40] Certain depancreatized herbivora such as the goat fail to develop the syndrome of diabetes and present normal glucose utilization *without excessive protein breakdown or ketone production*[41] Insulin serves in such instances only to mediate the storage of carbohydrate as fat, manifested as weight gain

Fatty Acid Synthesis from Glucose — According to Stetten[4] only 3 per cent of the dietary glucose of the rat becomes glycogen, while 30 per cent is used to synthesize fatty acids The latter mechanism is *reduced* drastically in the *diabetic* animal to only 5 per cent of the normal rate (0 1 gram instead of 1 9 grams of fatty acid synthesized daily from dietary carbohydrate)[42] Insulin abolishes this defect in synthesis The quantity of glucose not utilized because of this failure of fatty acid synthesis can *be recovered* from the urine in the same order of magnitude These observers calculate that 5 grams of glucose are needed for the manufacture of 2 grams of fatty acid They believe that the *decreased fat* stores of the untreated *diabetic* patient indicate 1) excessive mobilization and degradation of the fat reserves to make up for the inability to derive sufficient energy from glucose and 2) marked reduction in fatty acid synthesis at the expense of dietary glucose However the capacity of the obese diabetic to maintain or even gain weight without insulin indicates the mild nature of *this* metabolic defect in such a patient

The liver is not entirely responsible for the formation of new fat from carbohydrate *adipose tissue* may assume this role during recovery from fasting and after excessive carbohydrate ingestion or insulin administration[44] The finding of glycogen in adipose tissue under these circumstances[45] and its isotopic conversion to fatty acids[46] also indicate an extrahepatic site for this metabolic pathway Adipose tissue like the metabolism of fat has proven to be dynamic and not static Not only can it interconvert the higher fatty acids but it can also synthesize them from short chain fatty acids[47]

Gluconeogenesis from Fat — The long-disputed *conversion of fat to carbohydrate* has recently been resolved in favor of this process in a limited manner Not only the short chain fatty acids acetic and butyric acids[48,49] but also those with long chains as palmitic acid[50] may participate in glycogen and glucose formation *via* 2 carbon (acetate) fragments This may seem incompatible with the role of fat in ketogenesis but the replacement of carbohydrate by acetate formed from fat cannot increase the total glycogen present in the organism In the oxidative passage through the dicarboxylic acid cycle acetate requires partially oxidized fragments derived from *glucose* as catalysts[51] The energy arising from the formation of acetate by fatty acid is much less than that of the CO_2 producing com

from day to day and is determined by many factors besides the concentration and quantity of the ingested sugar. Of the 3 monosaccharides, galactose is absorbed most rapidly and fructose least rapidly, with glucose somewhere in between.[80]

Glucose and all the intermediates of the glycolytic cycle including lactic acid form the main source of liver glycogen. In addition to the latter organ, Reinecke[4] observed that the kidneys could be a source of some blood sugar in the eviscerated rat. Whereas glucose of dietary origin is the major source of liver and muscle glycogen in the normal animal, glycogenesis in the diabetic animals proceeds mainly from intermediate fragments smaller than glucose.[43] One-fourth to one third of the urinary glucose excreted by the diabetic animal is of synthetic origin.[43]

Fructose is converted by means of the hexokinase reaction to glycogen *via* glucose-6-phosphate mainly in the liver. Only a small fraction is converted to glucose by the intestinal mucosa.[73] Probably the failure of liver isomerase to convert fructose-6-phosphate to glucose-6-phosphate accounts for the condition of *essential fructosuria* in which disposal of ingested fructose is impaired. The kidney has also been shown to form some glucose from fructose.[4] Fructose is ineffective against hypoglycemia[74] contrary to earlier evidence suggesting such effect.[3] It cannot be diverted for tissue use appreciably before conversion to glycogen and appears to form liver glycogen more rapidly than glucose.[77] The disposal of fructose or its entry into tissues is *not* dependent upon insulin for the tolerance to intravenous fructose in the untreated depancreatized dog is normal.[13]

Galactose requires conversion to glucose and then glycogen by the liver before utilization. This is accomplished by a specific galactokinase and co-enzyme.[81] A normal galactose tolerance curve is found in diabetic patients with little or no apparent effect on the blood galactose level after insulin.[78] The entry of galactose into the cells of eviscerated animals is enhanced by insulin.[192] In the rare congenital anomaly *galactosemia* failure of the hepatic enzymatic conversion of galactose becomes apparent after the ingestion of milk by the infant. Mutually antagonistic effects of glucose and galactose are demonstrable, the administration of either hexose producing a fall in the blood level of the other.[79] Apparently both sugars act competitively on a common metabolic mechanism in a damaged liver.[79] Because the liver responds to the *total* combined blood sugar level, not to that of glucose alone, by a decreased release of glucose, hypoglycemia develops. This is analogous to Soskin's[80] demonstration by direct measurement of the release and uptake of glucose by the liver in response to the blood sugar level. Omission of milk from the diet leads to disappearance of the clinical manifestations and the restoration of a normal blood glucose pattern.

INTERMEDIARY METABOLISM OF FAT

The function of insulin in the synthesis of fat[43] and the role of the latter in the production of ketosis both in the diabetic and non-diabetic individual indicate the importance of the actively dynamic intermediary metabolism of fat. Normally, when carbohydrate is available, fatty acids are

These have disappeared since the introduction of protamine zinc insulin and nutritionally adequate diets

Recently Chaikoff and Forker[60] found it impossible to maintain positive nitrogen balance in diabetic dogs with less than 8 units per day, 16 units being required The changes appeared entirely in urea production although some extra nitrogen probably arose directly from amino acids, resulting in a net loss of body protein They found the nitrogen balance to be related almost linearly to the amount of insulin injected

Amino Acid Metabolism in Diabetes — A specific effect of insulin in decreasing the amino acid level of the blood in normal and diabetic subjects[62] was first noted in 1924 independent of its effect on the negative nitrogen balance in diabetes[61] A normal plasma amino acid level has been generally found in diabetes[63] In untreated severe diabetes Luetscher,[64] however obtained greatly elevated levels associated with a four to tenfold increase in urinary amino acid excretion This could not be correlated with the degree of acidosis or changes in blood sugar level Within a few hours after treatment with insulin had been initiated the amino acid level returned to normal and remained fairly stationary thereafter

That the usual role of the liver in protein metabolism could not be implicated in this effect was demonstrated by Mirsky[65] in obtaining the same reduction after insulin in the *eviscerated* animal an effect potentiated by anterior pituitary extract[66] Apparently insulin directly increases the rate of amino acid utilization for protein synthesis in muscle This *protein anabolic function of insulin* has been established definitively by the determination of the 10 essential amino acids in skeletal muscle and finding their concentration to be directly proportional to the quantity of each amino acid removed from the circulating blood after insulin administration[67]

Gluconeogenesis from Carbohydrate —Carbohydrate constitutes 50 to 60 per cent of the total caloric intake of the average American diet The polysaccharide starch the disaccharides sucrose and lactose and the monosaccharides glucose fructose and galactose are the only important forms of dietary carbohydrate Degradation to the monosaccharide stage by the usual processes of digestion is essential for final absorption and utilization

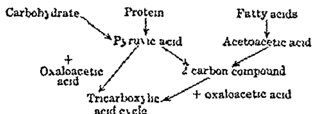
Sucrose may be an exception according to Rabinowitch[68] in that its ingestion yields a rise in blood sugar level within a few minutes before appreciable hydrolysis to glucose and fructose can occur This corresponds with well recognized clinical observations as to the prompt effect of ordinary table sugar in *relieving hypoglycemia in the insulin treated* diabetic patient The metabolism of sucrose cannot be explained entirely by that of its constituent monosaccharides Production of a longer chain glycogen molecule than occurs from either glucose or fructose is claimed for sucrose[69]

Absorption of the 3 hexoses represents a combination of simple non specific diffusion and more important specific *phosphorylation*[30] by the intestinal mucosa A small but definite amount of glucose is absorbed probably through diffusion by the human stomach[70] Maximum glucose absorption is confined mainly to the duodenum in man (with a capacity of 20 grams per hour)[1] the smaller residue being absorbed by the jejuno ileal region[2] The rate of absorption varies within the same individual

in situ necessary for the activation of fatty acid oxidation. In the liver he was able to demonstrate such coupling to another specific one step co-oxidation, that of alpha ketoglutarate to succinate.[95] Furthermore each molecule of acetoacetic acid yields 2 of citric acid in kidney tissue[2] and liver slices.[96] Mention has been made of the fact that fatty acid oxidation cannot increase the total glycogen stores since in the process of coupling some carbohydrate derivatives are used in order to provide the energy for the reaction.[62] The influence of insulin on coupling was also cited.[6]

"Acetate" Metabolism.—Recently 2 distinct species of 2-carbon units have been suggested by isotopic studies of acetoacetic acid formation during fatty acid oxidation.[97] This may explain the differences of opinion which exist as to the exact nature of "acetate."

Since the Krebs cycle involves the oxidation of pyruvic acid to a 2-carbon *compound prior to condensation with oxaloacetic acid and since 2 carbon* fragments participate in the synthesis of acetoacetic acid in fatty acid oxidation,[61] it is probable that an active *2-carbon ("acetate") compound* serves as the link in the metabolic pool common to carbohydrate, fat and *part of protein metabolism.*



In the final breakdown to CO_2 and water, pyruvate derived from glucose and "acetate" derived from fatty acids follow the same route.

Acetate is most rapidly metabolized by liver, kidney and muscle tissues.[98] In heart muscle it is readily converted to CO_2.[99] Only in liver tissue must it first pass through condensation to acetoacetic acid before oxidation.[98] No evidence exists that brain tissue can use acetate. Smyth[98] estimates *that the total possible energy production from oxidation of acetate could* equal that of glucose and therefore might easily represent another "quick fuel." The extremely rapid tissue utilization of acetate prompted Mudge and his associates[134] to use *sodium* acetate as a source of fixed base in paren*teral therapy of diabetic acidosis with success. Finally, it serves as the* important precursor in the formation of cholesterol, the steroid hormones, uric acid, and the porphyrins.[5]

Ketone Metabolism.—The ketone bodies, acetoacetic and beta hydroxybutyric acids, are *no longer regarded* as abnormal unoxidizable metabolic products but are considered to be the normal end products resulting from hepatic fatty acid oxidation. Produced almost entirely by the liver,[6, 66] they are oxidized finally and completely by all tissues[57] with the possible exception of the brain,[111] without obligatory coupling to carbohydrate utilization[94] or the influence of insulin,[89] even in the diabetic.[113] Ketonemia itself does not inactivate insulin[114] or impair the utilization of carbohydrate. The utilization of ketone bodies increases with rising blood concentration

oxidized *directly* by the tissues,[54] a process accounting for the major part of the energy derived from fat Degradation of fatty acids to the 4-carbon *ketone* bodies, acetoacetic and beta-hydroxybutyric acids, was first demonstrated as occurring *only* in the liver by the early work of Embden[55] Snapper[56] and their associates The latter also proved that muscle tissue normally used the ketone bodies for energy [57] This second pathway of fat oxidation to ketones assumes increasing importance in the liver during fasting and in diabetes mellitus The fasting human subject derives as much as 90 per cent of his energy requirements from the oxidation of fat of which less than half arises from the peripheral tissue oxidation of the the ketones [58] The latter mechanism accounts for only 30 per cent of the total fat metabolism in the diabetic patient [58] The extrahepatic oxidation of either fatty acids directly or of their intermediates, the ketones produced by the liver is completely *independent* of carbohydrate metabolism[58, 84] or the influence of insulin [89] In summary fatty acid oxidation directly by the peripheral tissues without the intervention of ketone production is the normal and usual method whereby the body supplements its energy requirements in the face of the limited stores of carbohydrate [36] The alternative route fatty acid → ketone formation in the liver → peripheral tissue oxidation appears normally to a minimal degree but is exaggerated either by a decreased liver glycogen reserve or by increased fat metabolism The *hyperlipemia* of diabetic ketosis is indicative of the increased mobilization of fat from the depots to meet the excessive demands for this source of energy

Fatty Acid Oxidation —Originally the beta-oxidation theory of fatty acids supposed that these substances broke down by the serial release of 2-carbon units until one 4-carbon residue remained in the form of ketones such as acetoacetic and beta hydroxybutyric acids which were regarded as waste products [90] Subsequently more ketone bodies were found per molecule of fatty acid oxidized than could be explained by this process and the theory of multiple alternate-oxidation supplanted it with fragmentation of the entire length of the fatty acid chain into 4-carbon units which easily formed ketone bodies [91] Because of discrepancies unexplained by this theory MacKay[9] and his associates proposed the beta-oxidation condensation hypothesis by which 2-carbon fragments were released from the fatty acid chain by classical beta-oxidation but these then condensed at random to acetoacetic acid A reconciliation of the different theories was obtained by Medes and her coworkers[93] by isotope technic indicating that in the liver a major portion of fatty acid oxidation (76 per cent) occurs through fission and immediate condensation of *2-carbon fragments* into ketone bodies while a minor amount (24 per cent) takes place by direct ketone formation from the final 4-carbon residue as in Knoop's original proposal [90]

Coupling with Carbohydrate Oxidation —Lehninger's[31] demonstration of the importance of phosphorylation by the ATP system in fatty acid oxidation was soon followed by his observation that such oxidation occurred in muscle in the absence of ATP if *coupled* with simultaneous fumarate oxidation in the Krebs tricarboxylic acid cycle [84] This coupled oxidation with that of carbohydrate is essential since the latter generates the ATP

in diabetic patients sometimes precipitated ketosis and coma in the pre-insulin era making the administration of carbohydrate imperative. Today the insulin-treated diabetic patient faces the same factor of starvation-induced ketosis when severe vomiting occurs.

The Role of Glycogen Reserve in Ketosis.—In diabetes the glycogen content of skeletal muscle is not greatly depleted while that of heart muscle and brain appear to be static.[109] The well known *severe glycogen depletion* which occurs in the *liver* in untreated diabetes[103,110] has been demonstrated in the human being directly through biopsy study.[111] By these observations in man Bondy and Sheldon[111] also confirmed the rapid effect of *insulin* therapy in *restoring* the glycogen content of the liver noted in the experimental animal. Since glucose alone will also enhance glycogen deposition in liver *and* muscle in the diabetic[107,103,112] the effect of *insulin* appears to be in the nature of *accelerating* the *rate of glycogenesis*[22] or *inhibiting glycogenolysis* still more.[114] Insulin enables the tissues to do at low or physiologic sugar concentrations that for which they would otherwise require very high sugar concentrations.[24]

In alloxan-diabetic rats glycogen *synthesis* appears to be impaired generally[114] while glycogenolysis is increased only during acidotic coma.[115] Liver glycogen is depleted not because glycogenesis is retarded but because glycogenolysis surpasses it. When the latter is proceeding at an accelerated rate the essential action of insulin becomes apparent as that of inhibition of the glycogenolytic process.[117] Direct catheterization of the hepatic veins in patients with diabetic ketosis reveals that the increased hepatic glucose output cannot be explained merely on the basis of glycogenolysis because of the already depleted glycogen content as determined from biopsy study.[56] It can be accounted for however almost entirely by protein breakdown as indicated by the increased urea production. The latter is rapidly arrested by insulin administration even before the excessive hepatic glucose output is reduced.[56]

The untreated depancreatized dog or cat may not present significant ketosis or diabetic coma except after depletion of liver glycogen following phlorizin administration.[125] Typical diabetic coma develops in the untreated depancreatized monkey only after starvation.[116] Mirsky and his coworkers[23] attempted to gauge the "severity" of diabetes by determining the *susceptibility* of patients to ketosis. Glycosuria was induced by the administration of phlorizin. When the glycogen reserve of the liver was adequate as in normal adults the blood sugar level remained constant and no ketonemia ever appeared. Diabetic adults on the other hand displayed evidences of inadequate reserves of liver glycogen in both "mild" and severe" cases without relation to their insulin requirement. Loss of relatively small amounts of sugar from the blood stream resulted in further deprivation of liver glycogen with consequent development of *hypoglycemia* and *ketosis* in about one-half the diabetic adults. The same phenomena were observed in one third of the normal children and two-thirds of the diabetic children. The younger the child the greater the susceptibility to ketosis a relation to age previously noted in animals.[40]

The administration of *carbohydrate* in the form of sweetened orange juice on retiring the night before the test or at 3 A.M. resulted in a *reduction*

until a maximum rate of 10 mM per liter is reached.[109] Heart muscle is the only tissue in which ketosis is associated with increased glycogen deposition.[110] Stadie[93] *demonstrated that when the demand for calories from fat oxidation exceeds 2.5 grams per kgm. per day, ketone bodies are formed in excess by the liver, beyond the capacity of the peripheral tissues to oxidize them*, thereby resulting in ketonuria. This not only wastes part of the catabolized fat in the *form of incompletely oxidized ketone bodies* but the accumulation and excretion of these substances leads to the syndrome of *diabetic ketosis and acidosis*.

The production of ketone bodies is dependent on the material at the disposal of the liver. The stimulus for increased fatty acid oxidation in the liver and the consequent acceleration of ketone body formation is *derived from a decreased glycogen reserve* associated with increased gluconeogenesis from protein. This may occur in response to starvation or in diabetes. The administration of either carbohydrate which stimulates glycogen synthesis, or insulin which induces glycogen retention in the liver *abolishes the excessive metabolism of fat*. It has been postulated that glycogen and fat compete for the same oxidizing systems in the liver[101] which have a preferential affinity for glycogen over fat, possibly because of the former's higher energy yield.[52] Depletion of the glycogen concentration, however, surrenders the substrate competition to the much larger stores of fat for oxidative purposes.

Effect of Carbohydrate on Ketone Production.—The untreated depancreatized dog can synthesize glycogen when treated with adequate amounts of glucose.[10, 103] Intravenous administration of large amounts of glucose *to diabetic animals not receiving insulin* results in a rapid fall in ketone body concentration of the blood and urine.[104] Himsworth[105] demonstrated this phenomenon in untreated diabetic patients in whom the ingestion of 50 grams of glucose resulted not only in the anticipated increase of hyperglycemia but also in a marked *decrease* in urinary ketones and nitrogen. In fact, an *excessive carbohydrate* intake or "spree" usually invoked by many physicians as a precipitating cause for diabetic coma has been actually demonstrated as *inhibiting* ketogenesis.[106]

The *use of glucose in the treatment of diabetic ketosis and coma* has been the subject of great controversy. On the basis of the depleted glycogen stores and meager total carbohydrate reserve of the diabetic patient in severe ketosis, Soskin[36] and Peters[53] have vigorously defended the program of additional parenteral glucose administration in order to potentiate the effect of insulin in the treatment of ketosis. In a meticulous balance study on this subject, Conn and Bauer[107] proved the benefit of continuous glucose administration in arresting the excessive ketogenesis of diabetic coma. When the minimal insulin requirements had been established the administration of glucose resulted in increasing retention of carbohydrate for oxidation *and storage* with consequent reduction in ketone production.

A therapeutic dilemma faced the physician in the Naunyn era of diabetes because the *starvation regimen* reduced glycosuria but led to ketosis which responded only to carbohydrate. Therefore a compromise was effected by alternating fasting or "green vegetable days" with high carbohydrate "oatmeal or potato days." The sudden institution of starvation treatment

coma He also noted that insulin treatment of benign non-diabetic glycosuria mistaken for diabetes mellitus may further distract the observer from the true diagnosis because of the acetonuria which follows hypoglycemia

Ketone Bodies in Blood and Urine — Although acetoacetic and beta hydroxybutyric acids are interconvertible in their formation *acetone* is the product of irreversible decomposition of acetoacetic acid[52] In diabetic ketosis acetone represents about 25 per cent of the total ketone body content of the blood and passes into the urine and expired air by the simple process of diffusion[135,136] The major portion of the blood ketone bodies consists of the 2 acids with the plasma containing beta hydroxybutyric acid predominantly while acetoacetic acid is confined mainly to the corpuscles[12] There is no correlation between the blood ketone level and the carbon dioxide combining power[140] *or the degree of hyperglycemia*[106]

As the blood ketone levels (normally 0 5 mg per cent or less) rise to as much as 360 mg per cent[141] their urinary output also increases[137] (to 40 grams or more in twenty four hours[142]) except in the presence of renal failure[137,139] A diminution or disappearance of urinary ketone bodies in the patient with diabetic coma may not signify clinical improvement but rather the further impairment of renal function In such instances the discrepancy between the continued strongly positive acetone odor to the breath and the minimal or negative urinary findings portends serious circulatory collapse Therefore Briggs[110] recommends the use of a simple technic of measuring acetone in the expired air for the estimation of the course of the ketosis comparing the degree of turbidity obtained by breathing into ordinary alkaline Nessler s reagent with that produced by known quantities of acetone

Whereas acetone is excreted in the urine as a non threshold substance beta hydroxybutyric acid has been said to have a renal threshold of over 20 mg per cent[137] Visscher[138] however in opposing the latter concept reports a gradual rather than a precipitate increase in the rate of excretion with rising plasma levels of beta hydroxybutyric acid an appreciable excretion occurring at plasma levels of 5 mg per cent

Blood Lipids in Ketosis — When the diabetic patient *utilizes* an adequate *amount of carbohydrate the lipid metabolism appears to be normal*[53] *In* diabetic ketosis however extreme *hyperlipemia* is usually noted due to the increased mobilization of fat from tissue depots in order to supply the energy needs of the body from fatty acid and ketone body oxidation Hemoconcentration in ketosis tends to elevate the serum lipid values still further When corrected for hemoconcentration the hyperlipemia of diabetic coma is found to consist mainly of a rise in *fatty acids* principally those belonging to neutral fat[143] The plasma cholesterol[143] and phospholipids[144] are *not* elevated Since phospholipids determine the stabilization of serum lipid emulsions[145] their failure to increase along with the fatty acids accounts for the clinical observation of gross *lipemia* during diabetic acidosis and its rapid disappearance after insulin therapy In malnourished patients deficient in fat stores *hypolipemia* may be observed during diabetic ketosis with hyperlipemia appearing after treatment has improved the nutritional state[53]

of the incidence of ketosis in diabetic children by 50 per cent.[11] This recalls the rather frequent finding of acetonuria in the early morning pre-breakfast specimens of juvenile diabetic patients particularly in the days before protamine zinc insulin. The prolongation of activity of this insulin through the night fast in addition to the prescribed practice of a snack on retiring have caused this catabolic phenomenon to disappear.

Insulin Insufficiency and Ketosis.—Upon deprivation of insulin some diabetic patients rapidly develop ketonemia and increasing hyperglycemia culminating in ketosis and precoma in twenty-four hours, while other, apparently similar patients can undergo this procedure even for one week without appreciable ketosis.[106] *In the latter group of patients the slowly* developing acetonuria can be prevented by large amounts of carbohydrate in the absence of insulin because glycogenesis is adequate. This is not true of the first group in whom glycogenolysis outstrips synthesis in the absence of insulin so that ketosis ensues rapidly no matter how large the amount of carbohydrate administered.

Insulin insufficiency is the *sine qua non* initiating diabetic ketosis regardless of the mechanism responsible for its *increased need* (*e.g.*, infection, trauma, nonspecific stress, *etc.* (*See* preceding chapter). This is augmented by:

1) The *decreased* synthesis of *liver glycogen* following infection[1,8] and the *increased glycogenolysis* induced by toxemia.[1,9]
2) The *increased protein catabolism* due to adrenal cortical[118] and ACTH activity following a great variety of nonspecific stresses.
3) The *increased ketone body production* specifically caused by ACTH[139] elaborated in the course of the same stresses.

The rate of urinary excretion of corticosteroids during diabetic ketosis is 2 to 8 times as rapid as after recovery, the increase not becoming apparent until mild acidosis sets in.[123]

Recently the administration of testosterone propionate (150 mg. daily) to a patient with moderately severe diabetic ketosis resulted in the reduction of ketonuria from 5 grams daily to negligible amounts.[108] This effect was *supposedly mediated through primary inhibition of pituitary adrenocorticotropin production with secondary but specific decrease in keto*genesis, gluconeogenesis from protein being excluded by reason of a simultaneous decrease in urinary nitrogen excretion.

Insulin Hypoglycemia and Ketosis.—The inhibition of hepatic glycogenolysis by insulin may be followed by a *reversal* of this action when *hypoglycemia* supervenes.[117] The compensatory mechanisms such as the release of epinephrine evoked by hypoglycemia lead to an increased rate of hepatic glycogenolysis which in itself suffices to accelerate ketogenesis irrespective of the glycogen content of the liver.[117] Furthermore insulin hypoglycemia will increase protein catabolism in answer to the increased need for new carbohydrate, a phenomenon markedly accentuated by the secretion of the adrenal cortex, the stimulus for which is hypoglycemia itself.[118] Clinical confirmation of these observations was made by Drey[119] in pointing out the frequent recurrence of transient acetonuria associated with hypoglycemia some time after intensive insulin treatment for diabetic

to 300 mg per minute.[149] Therefore an *excess glucose load* (plasma glucose content × glomerular filtration rate) over renal tubular reabsorptive capacity results in glycosuria.

Concentration by the distal tubules of the unabsorbed glucose permits the excretion of considerable amounts *without polyuria* if the maximum osmotic limit is not exceeded.[15]

In a metabolic study performed at the Russell Sage Institute of Pathology, Tolstoi and Weber[154] found that insulin treated diabetic patients could excrete as much as 100 grams of glucose and more in 1 liter of urine and remain free of thirst and polyuria, as well as acetonuria and protein catabolism. This was also noted in the pre-insulin era, for von Noorden[154] recorded an instance of 64 grams of glucose excreted in 1600 cc. of urine.

Diuresis.—Glycosuria leads to polyuria and diuresis in the treated diabetic patient when the total glucose excretion exceeds the osmotic limit of renal tubular concentration. Butler and his associates[17] have shown that in diabetic *ketosis* the kidney *cannot* concentrate urine to the normal level. In the presence of insulin insufficiency the excretion of salt and other electrolytes reduces the absolute amount of glycosuria needed to provoke diuresis since the total solute concentration rather than the level of any one solute determines the maximum osmolarity of the urine.[163] An irreducible minimum of water is required for the excretion of each solute. The urinary loss of sodium and chloride increases fourfold during nonketonic diuresis, while potassium and phosphate are unchanged.[16, 158] Furthermore, the diuresis following the marked loss of sodium chloride which occurs in diabetic ketosis causes an increase in glycosuria.[152, 154] An excessive *urinary loss of intra- and extracellular electrolytes* occurs in diabetic ketosis, independent of diuresis and polyuria, with both factors assuming extreme proportions as the severity of the condition advances.

Acidosis.—The decrease in plasma bicarbonate and the lowering of plasma pH characteristic of diabetic acidosis result from:

1. Accumulation of ketone acids at the expense of bicarbonate.
2. Loss of base with the urinary excretion of the ketone acids[6, 17] and phosphate.[18] Total base is also lost by the excessive urinary excretion of chloride.[16, 17]
3. Reduction in the intracellular buffer system of organic phosphoric esters with their breakdown in red blood cells and the liberation of inorganic phosphate.[158]

In stage 1, before an actual deficit or loss of base has occurred, the administration of insulin and carbohydrate alone will be sufficient to overcome acidosis by inhibiting the formation and accelerating the excretion of the ketone bodies which have displaced bicarbonate. Actual replacement of base, principally sodium, becomes necessary when ketosis is severe or protracted.

The *compensatory mechanisms* available for the saving of base and minimizing acidosis include:

1. Respiratory excretion of CO_2 by hyperpnea.
2. Renal excretion of ketone bodies in free titratable form and acidification of the urine.
3. Increased renal production of ammonia.

THE DERANGEMENTS IN DIABETIC KETOSIS, ACIDOSIS AND COMA

In the light of the preceding discussion the sequence of events leading to the development of diabetic ketosis, acidosis and coma proceeds as follows in steplike progression according to Guest[131]

1. *Insulin insufficiency*
2. *Impaired glycogenesis increased glycogenolysis* hyperglycemia glycosuria diuresis
3. *Increased hepatic ketogenesis* ketonemia ketonuria
4. *Metabolic acidosis* decreased base and pH of body fluids hyperpnea peripheral vasodilatation and collapse
5. *Increased cellular catabolism* liberating protein nitrogen inorganic phosphates potassium *etc*
6. *Loss of electrolytes* by increased urinary excretion and vomiting, and therefore decreased electrolyte concentration in extra and intracellular spaces
7. *Dehydration* leading to hemoconcentration decreased blood volume fall in blood pressure shock decreased kidney function and anuria
8. *Tissue damage* resulting from increased cellular catabolism, anoxia acidosis and ketosis
9. *Coma* resulting from cerebral anoxia ketonemic narcosis and acidosis

Hyperglycemia — The hepatic origin of the blood sugar and its regulation by the homeostatic mechanism of the liver[80] have been described above Despite the depletion of its glycogen in diabetes the liver pours forth a flood of glucose derived from other sugars protein and other non carbohydrate precursors Although glycogen deposition in liver and muscle[102 103] and the rate of glucose utilization by the peripheral extrahepatic tissues[17] are increased by the hyperglycemia itself their effect in reducing the blood sugar level is far outstripped by extravagant glycogenolysis and gluconeogenesis The *height* of the blood sugar level bears *no* relation to the severity of ketosis[53 106 131] and may fall considerably when coma has been prolonged to the point of exhaustion of all possible sources of carbohydrate[131] In the pre-insulin era starvation therapy of diabetic coma at times led to death in hypoglycemia![146]

Glycosuria — Glycosuria reflects not only the metabolic phenomena which produce hyperglycemia but also the function of the kidney as determined by the rates of glomerular filtration and tubular reabsorption[150] The glomerular filtrate consists of plasma water containing glucose in the same concentration as in plasma This is subjected to selective reabsorption in the proximal convoluted tubules by phosphorylation[147] followed by the release of dephosphorylated glucose back into the circulating blood through the action of phosphatase[148]

Nı and Rehberg[1 1] found that glycosuria appears when more glucose is presented to the tubular cells than can be reabsorbed The sugar is not reabsorbed in constant concentration the percentage *increasing* with the degree of hyperglycemia However the increase in reabsorption does not parallel the increase in glucose filtration and consequently more and more is excreted The normal limit of tubular reabsorption of glucose is 300

b) *Phosphate Store Depletion* — The intracellular buffer systems of the erythrocytes are *more important in maintenance of plasma pH than* the buffers of plasma.[168] While hemoglobin is the most potent of the intracellular buffers, the phosphoric esters are more flexible in their wide limits of change in concentration for the same purpose. They represent an appreciable portion of the total ionic concentration within the cells and influence the distribution of diffusible anions between cells and plasma as well as the transfer of mineral cations such as potassium through the enzymatic reactions of phosphorylation.[168]

These organic acid soluble phosphorus compounds (normally 50 to 60 mg per 100 cc of packed cells) consist of ATP, hexose phosphates and diphosphoglycerate and constitute a labile store of phosphorus for many anabolic and catabolic processes which involve the transfer of phosphorus. *They are synthesized and decomposed in the course of* the glycolytic cycle of carbohydrate metabolism with decomposition being favored when the pH shifts to below 7.3.[169]

In *diabetic coma* there is a profound breakdown of the labile organic phosphate esters with marked *reduction* in *concentration* in the red blood cells and an increased *liberation of* inorganic phosphate into the plasma.[168] The latter leads to the *phosphaturia* common in diabetic coma.

The net result of intracellular catabolism is to *deplete* the tissue stores of K and P, although this may not be apparent on *initial* examination in diabetic acidosis *before treatment* when their blood levels are usually *elevated* or *normal*.[170, 171] Again, no correlation exists between the level of blood sugar and that of potassium or inorganic phosphate.[171]

Loss of Electrolytes — *Diabetic acidosis and coma represent the extreme* clinical expression of electrolyte and water loss. When the stage of *uncompensated acidosis* has been reached insulin administration is incapable of establishing recovery without the physiologic replacement of the various deficits in water, sodium, potassium, chloride and phosphate. The *direction* and the *rate of changes* in these constituents of blood and urine reflect the underlying tissue alterations more accurately than any isolated determinations at one given time.[168] A 10 per cent loss of body weight on *the basis of dehydration* alone means a 14 per cent loss of body water, a *23 per cent* loss of extracellular water and electrolytes and a 10 per cent loss of intracellular water and electrolytes.[173] The magnitude of these losses is increased markedly in diabetic coma by the additional factors of *starvation* (further nitrogen breakdown), *vomiting, diuresis* and excessive *excretion of base* combined with the ketone bodies (sodium) or independently (potassium).

Sodium and Chloride — A marked loss of sodium chloride into the urine was first noted by Atchley and his coworkers[56] at the very onset of ketosis. Ninety per cent of the total electrolyte content of normal serum consists of *sodium* salts, principally *chloride* and *bicarbonate* (over 90 per cent).[174] The importance of sodium derives not only from its predominance as the major electrolyte quantitatively, but also because its movements into and out of the cells determine osmotic equilibrium and water balance. The

These systems have serious limitations however. Hyperpnea involves severe muscular effort and contributes to eventual dehydration because of the increased loss of water vapor in expired air.[131]

The excretion of the ketone acids in *free form* has been shown by Pitts[159] to be extremely limited because these are relatively strong acids in comparison with monobasic phosphate and therefore must in large part be combined with fixed base. Ordinarily the kidney can excrete 4 to 5 times as great a quantity of weaker buffer acids. For each millimol of beta hydroxybutyric acid excreted as such the kidney salvages only one half a milliequivalent of base.[160]

The renal mechanism of acidifying the urine by excreting sodium as sodium monophosphate has been demonstrated not to save base at all contrary to previous concepts. In restoring 0.8 milliequivalent of base to the blood as bicarbonate this process is inefficient in that 1.0 milliequivalent of base is simultaneously lost in the urine.[160]

The substitution of *ammonia* for inorganic base to form salts of ketone acids is an inadequate device since its production during acidosis exhibits a certain inertia. It reaches maximum intensity only after several days (usually about 4) and continues at a high rate some time after disappearance of the acidosis.[161] Only when acidosis develops slowly can ammonia production be significant in conserving base.[162]

When dehydration, hemoconcentration and circulatory collapse develop in severe diabetic coma the excretion of ketone bodies and the formation of ammonia are reduced further or completely arrested as renal function fails.

Acidosis in itself is pernicious in further aggravating the existing disturbances of diabetic coma by

1. accelerating the catabolic processes in all tissues → decomposition of intracellular phosphorylated compounds[131]
2. interfering with kinetics of tubular reabsorption → increasing phosphaturia[160]
3. decreasing peripheral resistance → shock[163]
4. depressing cerebral oxygen consumption and function → coma[164]

There is little correlation between the degree of hyperglycemia and the blood bicarbonate content when acidosis is most extreme.[157]

Increased Cellular Breakdown.—The increased tissue catabolism in diabetic acidosis indicated by the marked *urinary excretion of nitrogen*[6] and amino acids[64] also involves the liberation of intracellular components, inorganic *phosphate* and *potassium* particularly, into the plasma and from these into the urine by excretion. Phosphaturia in diabetic coma has been recognized for many years. Atchley *et al.*[56] demonstrated that the loss of potassium and phosphate was in *excess* of the nitrogen excretion.

a) *Potassium Store Depletion.*—The human body contains 110 grams of potassium with about 75 per cent in the muscles and 3.6 per cent extracellularly.[172] The breakdown of tissue releases protein bound *potassium* within the cells[166] as proven recently by direct analyses of skeletal muscle biopsies.[167] Since potassium is deposited along with glycogen in the liver,[165] glycogenolysis also releases potassium to the plasma. Furthermore interference with the carbohydrate metabolism of the red blood cell leads to an outpouring of cell potassium.[168]

futile but inherently wasteful renal mechanism of excreting phosphate in order to save base[160] adds to the *phosphaturia*

Calcium and Magnesium —Despite increased calcium excretion in the urine during diabetic acidosis[56] the serum calcium concentration remains normal[179] Serum magnesium is either normal or elevated the latter being *found in comatose patients falling markedly after therapy*[179]

Dehydration —The severe electrolyte loss leads to dehydration with reduction in both extracellular and intracellular fluid content but to a greater magnitude in the latter Further loss of water occurs through polyuria and diuresis vomiting and hyperpnea Dehydration is most severe when *acidosis is protracted or develops slowly allowing for greater electrolyte loss*

The *basic* parenteral *maintenance* requirement for water in diabetic acidosis during the first twenty four hours of treatment has been estimated as 1500 cc per square meter of body surface according to Butler[150] In addition the *replacement* for dehydration requires almost *twice* as much[18]

Therefore the *treatment* of diabetic acidosis in an average-sized patient (150 pounds in weight and 67 inches in height) will require the administration of a minimum of *6 liters of fluid* (2700 cc for basic maintenance plus 3600 cc for replacement) and more

Dehydration leads to hemoconcentration diminished blood volume lowered blood pressure diminished renal function (rising levels of non protein nitrogen) and finally collapse and shock with anuria

Tissue Damage and Coma —Regardless of the intensity and diligence of therapy certain instances of diabetic coma fail to recover if the *duration* of coma if prolonged[181] The one generally accepted indication of a poor prognosis in diabetic acidosis is the finding of coma and unconsciousness *This is associated with an apparently unavoidable high mortality*[164 181]

No specific pattern of the chemical constituents of blood as treatment is begun helps to distinguish which patients recover or survive There is *no* correlation between the degree of acidosis as measured by the CO_2-combining power and the development of the comatose state[164] Providing *consciousness is retained eventual recovery is possible in spite of severe acidosis*

Irreversible changes in the vital organs brain heart and kidneys have been attributed to the effects of severe tissue dehydration shock with cellular anoxia acidosis and ketonemia Kety and his coworkers[181] found a *critical level for cerebral oxygen uptake below which consciousness disappears* and survival is almost impossible in patients with diabetic coma They found a 40 per cent reduction in cerebral oxygen consumption in diabetic coma

It is obvious that success in the treatment of diabetic acidosis revolves *around its prompt and early initiation before the onset of coma and failing that* vigorous replacement and supportive therapy before the duration of coma has lasted long enough to cause irreversible damage

The Metabolic Alterations During and Following Treatment —The administration of *insulin* overcomes the primary deficiency which initiates diabetic coma *thereby decreasing gluconeogenesis and hepatic glycogenolysis* hyperglycemia and glycosuria It increases the deposition of glycogen

central feature of clinical *dehydration* is a reduction of the extracellular compartment followed by a decrease in plasma volume. Intracellular sodium is equal to about one-fourth of total extracellular sodium[175] contrary to former belief and is transferable in and out of the cells.[176] A reciprocal relationship exists between intracellular sodium and potassium so that when the latter is decreased the former replaces it.[1 5]

The serum sodium in diabetic acidosis may vary from normal to an extreme deficiency depending upon the *intensity* and *duration* of the condition, the association of diuresis and vomiting and the degree of dehydration. Thirst leads to the drinking of large amounts of plain water which adds to salt depletion and dehydration while the common practice of gastric lavage in the initial treatment of diabetic acidosis *removes* more sodium and chloride from the body.[174] The renal mechanisms for the excessive sodium loss have already been described on the basis of diuresis[15-] impaired tubular reabsorption,[1 3] and combination with ketone acid[56 159] phosphate[158] and chloride.[157]

The loss of *chloride* in the urine and its serum concentration reduction exceed that of sodium.[58 157] Although excreted chiefly as sodium chloride the elimination of chloride as a neutral salt of ammonia detracts from the more useful purpose of the latter in sparing base by combining with the ketone acids.

Hypochloremia is a prominent feature of diabetic acidosis but why the chloride deficit far exceeds that of base is as yet unexplained. The vomitus contains no free hydrochloric acid in acidosis; in fact its content of base, sodium and potassium equals or exceeds that of chloride.[157] A relationship exists between chloride and potassium in that a deficit of one leads to a deficit of the other.[1 5]

Potassium.—The anorexia and vomiting which develop in the course of diabetic acidosis preclude any intake of potassium. In addition this electrolyte is lost as a result of vomiting.[157] Intracellular catabolism[166 167] glycogenolysis[16] and decomposition of the organic phosphorus compounds involved in carbohydrate metabolism[168] contribute to the depletion of potassium stores and subsequent *hyperpotassemia*. This leads to a considerable loss of potassium in the urine, a phenomenon observed even with low serum K levels because of the inability of the kidney to conserve it.[178] The enhanced urinary excretion of potassium is the result of tubular secretion[177] independent of glomerular filtration. Gastric lavage accounts for additional loss of potassium.[157 174] When acidosis accompanies diarrhea further depletion of the body stores of this electrolyte results from the fecal loss.

The initial values for serum potassium in diabetic acidosis are elevated or normal[171] despite the tremendous loss of this electrolyte. This may be partly accounted for by hemoconcentration and renal functional impairment.[1 1] No correlation exists between the level of blood sugar or that of serum potassium.[171] Dramatic alterations in serum and tissue potassium occur following therapy of diabetic acidosis.

Phosphate.—As with potassium the cellular catabolism of diabetic acidosis results in decomposition and depletion of its stores with migration into the blood of inorganic phosphate leading to elevated levels.[1 8] The

of insulin with or without parenteral glucose also increases the requirement for these accessory factors and thus leads to their relative or absolute deficiency[153,154] An increased blood level of pyruvate has been reported in diabetic acidosis as indicating thiamin deficiency[156] In *niacin* deficiency diminished cerebral *glucose utilization* associated with decreased oxygen consumption of the brain have been found to be correlated with the mental changes of pellagra[155] The comatose state of diabetic acidosis may be intensified by these effects of vitamin deficiency which could also explain the delay in the return of consciousness sometimes seen after apparently adequate chemical restitution

THE FUNCTION OF INSULIN

The action of insulin has long been a hotly disputed subject The following conclusions may be drawn from the preceding discussion on the metabolic derangements in diabetes mellitus

1 It is *essential* for the *synthesis of fatty acids* from carbohydrate
2 Its role may lie somewhere in the *glucose* ⇄ *glycogen* reaction but as yet *none* of the known enzyme systems involved in this cycle appear to be influenced by insulin directly The relation to the hexokinase reaction has not been corroborated It may participate in the reactions of the Krebs cycle directly enhancing the *coupling* between phosphorylation and oxidation
3 Its absence is *without* effect on the carbohydrate metabolism of certain tissues notably *brain* testis and erythrocytes
4 *Glucose utilization* and *glycogen synthesis* by the tissues proceeds even in the absence of insulin
5 However insulin enables glucose to participate in carbohydrate metabolism at lower concentrations than would otherwise be necessary *accelerating the velocity* of those reactions It increases the rate of entry of glucose into the metabolic cycle of the cell
6 It *inhibits glycogenolysis* in the *liver* of the diabetic subject *preventing ketogenesis* and *decreasing gluconeogenesis from protein*
7 *Tissue protein synthesis* from amino acids appears to be dependent upon the influence of insulin

Hormonal Control —The effects of the other endocrine secretions upon the actions of insulin and vice versa are discussed in the preceding and other chapters The *hormonal control* of the localization of the *site* of insulin action on the *surface membrane* of tissue cells is suggested by the recent work of Stadie and his associates[157] They demonstrated a rapid and stable *combination* of insulin with the intact normal muscle cell as the first step in its physiologic action before producing its metabolic effects This surface phenomenon was found to be impaired in diabetic tissue in direct correlation with the severity of the pre-existing diabetes Normal muscle cells could be rendered refractory to combination with insulin by crude anterior pituitary extracts both *in vitro* and *in vivo* A normal response was obtained however in muscle tissue obtained from adrenalectomized or hypophysectomized animals Insulin was found to be *without* effect however

in the liver (and muscles), thereby arresting ketonemia and ketonuria This may be sufficient in *compensated* acidosis to establish full recovery in mild or moderate states of diabetic ketosis

As acidosis continues it becomes *decompensated* due to the loss of base, electrolyte and water which *must be replaced parenterally in part or completely* This may be done by the administration of sodium chloride and water, and, if need be, potassium, phosphate and bicarbonate In the presence of falling blood pressure reduced kidney function or peripheral collapse, supportive measures such as whole blood transfusion are indicated

With regard to sodium chloride replacement three schools of thought prevail advocating either (1) *isotonic* saline solution, (2) *hypertonic* saline solution because of the major salt depletion[157, 174] or (3) *hypotonic* saline solution because of the huge water deficit [176, 180]

In the *post-acidotic phase of recovery*, the restoration of anabolic cellular function results in a slow uptake of electrolytes by the cells Rehydration causes an expansion of extracellular fluid volume producing a sharp *drop* in serum levels of *potassium* and *phosphate*, substances which represent intracellular components originally *Hypophosphatemia* is characteristic of the recovery period and the return to normal levels is delayed until long after treatment has been discontinued [158] The same fall and lag in recovery has been noted for magnesium [179] However, no apparent functional disturbances accompany these deficiencies

Potassium deficiency produces a unique syndrome in the course of recovery from diabetic acidosis as described originally by Holler [182] It is characterized by generalized muscular weakness and paralysis of the respiratory muscles associated with specific electrocardiographic changes The margin of safety for variations in potassium concentration is very narrow since a change in either direction of 2 milliequivalents may produce serious effects [174] Normally the serum concentration ranges between 3 1 to 5 3 milliequivalents per liter of serum Symptoms may appear with levels below 2 0 or above 7 0 milliequivalents

The fall in serum potassium level occurs *twelve to twenty four hours* after therapy has begun Then it rises gradually over a period of several days before reaching normal values The re expansion of the extracellular fluid volume which follows treatment reduces the level of serum potassium Any urinary excretion of potassium during recovery contributes to further hypopotassemia The movement of potassium into the cells occurs only when it is available from exogenous sources [171]

The initial administration of potassium early in the treatment of diabetic coma is unwarranted and hazardous in view of the high serum level at that time and the usually impaired renal function Furthermore the toxicity of a high serum potassium level is increased in the presence of such low serum sodium levels as develop during diabetic coma

Vitamin deficiency particularly of the components of B complex *thiamin, niacin* and *riboflavin* may develop in the course of treatment of diabetic acidosis Being water soluble their stores are probably already depleted by diuresis before treatment is begun Because of the essential role which these vitamins play in the glucose-oxidative cycle the sudden increase in carbohydrate metabolism which follows the administration of large doses

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on the *in vitro respiration* of skeletal muscle from normal subjects *and* diabetic patients [188]

The mild insulin requirements (20 to 40 units at the most) of the *totally depancreatized man* and his marked responsiveness to the action of insulin cannot be reconciled with the average clinical picture of diabetes mellitus or the above findings

Relation of Insulin to Sulfhydryl Compounds —Insulin contains a rather large amount of sulphur (3 3 per cent) in the form of cystine (12 per cent of its total weight) It contains no sulfhydryl groups When the disulphide linkage (S-S) is reduced to the sulfhydryl (S H) form insulin loses its activity

Since the beta cells of islet tissue appear to contain less sulfhydryl compounds than other tissues, it has been suggested that the diminution in these substances is due to their use as basic material for the synthesis of insulin a disulphide compound [189] Therefore any depletion of S-H groups such as follows the administration of alloxan and other oxidizing agents might decrease insulin synthesis [189] On the other hand cysteine glutathione and several other S H compounds afford protection against the diabetogenic action of alloxan *in animals* Thyroidectomy and thiouracil administration increase the free S-H groups in tissues and also protect the rat against alloxan effects [190] Application of these animal observations to *human* diabetes mellitus has yet to be established In fact according to Schoenbach and his associates [191] the S-H content of human serum is *not* altered definitely or significantly in a variety of metabolic disorders including diabetes

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Chapter 32

DIAGNOSIS OF DIABETES MELLITUS AND OTHER MELITURIAS

By Henry Dolger, M.D.

Definition.—The generally accepted definition of diabetes mellitus as an *impairment* of carbohydrate metabolism due to *insulin insufficiency* is *inadequate*. It should include the associated phenomenon of *premature vascular degeneration* as an integral part of the clinical syndrome.[1]

A number of different procedures may be employed for the induction of diabetes both experimentally and clinically through the production of relative or absolute insulin deficiency, *e.g.*:

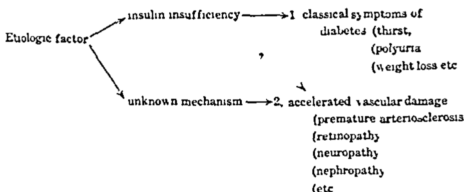
1. An absolute decrease in available insulin (severe intrinsic pancreatic disease and total pancreatectomy).
2. An increased need for insulin due to its increased utilization (over-feeding, obesity and hyperthyroidism).
3. An increase in the rate of insulin destruction.
4. A decrease in the responsiveness of the enzyme systems affected by insulin (endocrine factors such as purified growth hormone, crude anterior pituitary extract, adrenal cortical steroids and ACTH, and liver disease).
5. The production of insulin antagonists or neutralizing agents.

This recapitulation of the different possible etiologic mechanisms supports the classification of diabetes mellitus as a symptom complex and not a specific disease entity except for the relatively infrequent instances of pancreatic destruction or extirpation and adrenal cortical hyperfunction.

Whatever etiologic factors finally result in the manifestation of hyperglycemia and glycosuria, they must be operative in the pathogenesis of diabetes *long before* a disturbance of carbohydrate metabolism becomes obvious. The bearing of an excessively large infant frequently portends the future onset of diabetes in the mother. So-called diabetic complications are often fully developed by the time glycosuria or the classical symptoms of thirst and polyuria are noted. Although this is generally true of patients beyond middle age, even young adults may present evidences of premature accelerated vascular damage such as diabetic retinopathy, etc., without hyperglycemia and little or no impairment of glucose tolerance. This is further substantiated by Colwell's[2] ingenious calculations that diabetes has progressed through half its course by the time clinical recognition is effected.

Onset.—From the standpoint of dynamics, diabetes mellitus may be conceived as comprising two distinct groups of manifestations developing at different rates of speed.

Observation of totally depancreatized human beings over a period of the next twenty years will prove whether simple insufficiency of insulin alone can be responsible for the degenerative changes. In the average case of diabetes mellitus this relationship is obscured by possibility of degenerative or catabolic effects arising *independently* from the as yet unknown etiologic factors. Arteriosclerosis, hypertension and diabetes mellitus may have a common origin with the causative agent provoking insulin insufficiency incidentally only in susceptible individuals.



The primary appearance of typical diabetic symptoms which characterizes the onset in all juvenile, most young adult and one-third of the older adult patients overshadows the insidious slowly progressive secondary degenerative changes for a number of years. With *increasing duration* of diabetes however the latter break through the unrecognized subclinical stage finally to produce a variety of clinical manifestations formerly regarded as complications. An average of about thirteen years duration of diabetes has been noted as the time of the first appearance of these secondary associated phenomena.[1] The disparity of primary and secondary manifestations at the *onset* and their fusion later in *young* diabetic patients may be depicted as follows

	Onset	*13 to 20 yrs later*
Symptoms of Insulin Insufficiency	+	+
Accelerated Vascular Damage	0	+

Classical diabetic symptoms *cannot* be elicited in *over 50 per cent* of middle aged and elderly patients when glycosuria is first discovered.[4] At this time many of the asymptomatic patients and about one-fifth of the group with diabetic symptoms already present evidences of accelerated vascular degeneration.[1] In fact the degenerative phenomena may precede the appearance of hyperglycemia and glycosuria.

The 3 types of *onset* of diabetes in patients *beyond middle age* may be depicted in contrast with that of younger individuals as follows

	Onset		
Symptoms of Insulin Insufficiency	0	+	+
Accelerated Vascular Damage	+	+	0

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1. An absolute decrease in available insulin (severe intrinsic pancreatic disease and total pancreatectomy).
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Onset.—From the standpoint of dynamics, diabetes mellitus may be conceived as comprising two distinct groups of manifestations developing at different rates of speed.

due to the increased intra abdominal pressure Several weeks elapsed before urinalysis revealed marked glycosuria

Enuresis is often the first clue to the diagnosis in children Unfortunately this may be regarded initially as a behavior disorder until the associated symptoms of weight loss and thirst indicate the true nature of the disease I have seen several youngsters whose recollections of the onset are unhappily associated with the corporal punishment inflicted by ignorant parents because of bedwetting

Thirst is consequent to the dehydration It may go unnoticed for a long time in patients who ordinarily drink large quantities of water tea or beer They usually attribute the polyuria solely to the large fluid intake Some patients unconsciously add to the existing disturbance imbibing enormous quantities of coke and 'soda pop in order to quench the insatiable thirst The diagnosis was completely overlooked in the case of a young girl until an unusually large bill for bottled water (the only potable supply available in that community) was presented to her father Another patient docilely submitted to elaborate nose and throat treatments ' for six months because of *pharyngitis sicca* ' which resolved completely when insulin was administered after the discovery of glycosuria

Hunger and *loss of weight* are noted in the severe diabetes of most children and a minority of adult patients Emaciation results from the depletion of fat stores tissue protein breakdown and marked water loss through diuresis

Asthenia and *somnolence* also reflect the catabolic state

The obese adult diabetic however often continues to *gain* weight despite moderate glycosuria indicating the relatively mild impairment of fat synthesis in such instances Diabetes may develop in the obese individual in the course of a prescribed weight reduction regimen The patient and physician may be gratified at first by the continued loss of weight despite the abandonment of the low caloric diet until other symptoms call attention to the existence of diabetes

Pruritus of a generalized nature is rather uncommon and is probably due to dehydration *Pruritus vulvae* almost as frequent a presenting symptom of diabetes as thirst and polyuria is not related directly to these symptoms or to the degree of glycosuria This is due to the fact that its cause is usually a monilia infection superimposed on local tissue changes of a pellagrous type[7] Marked disparity may exist therefore between the severity of diabetic vulvitis and glycosuria Often the latter is of minimal degree escaping detection in the analysis of urine obtained casually or in the fasting state The boiled ham appearance of the lesion is quite typical yet experienced gynecologists have been known to treat it locally for many months without success In sheer desperation a patient had consented to vulvectomy because of intractable pruritus when another gynecologist suspecting diabetes discovered glycosuria in a post prandial urine specimen

The same mycotic invasion of the skin accounts for the occasional intertrigo with anal and scrotal pruritus in the male

In addition to the above general symptoms recognized since antiquity certain manifestations of specific organ involvement are often evident as

Such differences in the clinical course account for the high incidence of unrecognized diabetes[5] and the finding of a "casual onset" or an "onset with complications" in 66 *per cent* of all patients[4] Only 34 *per cent* presented themselves because of "diabetic" symptoms[4]

Sudden onset (within twenty-four hours) of symptoms such as thirst and polyuria is extremely infrequent occurring only in about 1 3 per cent of cases[6] Obviously the mechanism of polyuria represents a stage of decompensation arising from glycosuria of some duration The relatively rapid onset of symptoms in juvenile diabetes reflects the limited glycogen reserve the marked susceptibility to ketosis and the severity of insulin insufficiency which characterize this group of patients

The *diagnosis* of diabetes mellitus, in the light of this discussion, cannot be limited merely to a few classical symptoms supported by *chemical* determinations of urine and blood sugar but must include *clinical* recognition of the generalized systemic manifestations of the disease

CLINICAL DIAGNOSIS

Certain pathogenetic factors are clinically significant as aids in the diagnosis of diabetes mellitus, particularly heredity obesity and disturbances of childbearing

A *familial history* of the disease is the most common and pertinent cause for arousing a suspicion of diabetes despite the absence of symptoms

The *past history* of the patient is equally important in eliciting such portents of diabetes as obesity the birth of oversized infants toxemia of pregnancy stillbirths and transitory "benign" glycosuria during pregnancy

CLASSICAL SYMPTOMS

These include polyuria thirst hunger pruritus weight loss and asthenia No single complaint occurred in more than 50 per cent of adult patients[4]

Asymptomatic glycosuria has been noted from two to eleven years before the average adult diabetic develops polyuria[4] In juvenile diabetes the asymptomatic interval is much shorter because of factors already discussed *Polyuria* and *nocturia* represent the decompensated stage of diabetes described in the mechanism of polyuria and are the commonest symptoms of all The voiding of a large volume of pale urine with a high specific gravity is characteristic of diabetic polyuria

It is surprising how long patients will tolerate disturbing polyuria without realizing its abnormality Failure to recognize the significance of this symptom is due in part to the term "diabetes mellitus" which is meaningless to most laymen Were we to restore the terminology of Willis "the pissing disease," it would obviously convey some inkling of the disorder to the unsuspecting public Some physicians have been carelessly diverted from the diagnosis of this complaint treating the patient for prostatism nephritis, etc One patient receiving pneumoperitoneum treatment for abdominal tuberculosis was assured that his severe polyuria was simply

Because of pain and loosening of the teeth patients may first seek dental attention when diabetic symptoms are absent or disregarded. The typical lesions which indicate the underlying metabolic disorder to the dentist include hypertrophied congested cyanotic gingivae marginal periodontoclasia diffuse alveolar bone resorption on x ray and gingival abscesses

Neurologic Manifestations — *Neuropathic* symptoms have long been recognized as the initial complaints of diabetic patients. The disturbances may be either subjective or associated with definite neurologic abnormalities. The former are usually noted along with classical diabetic symptoms and consist of generalized aching pains nocturnal cramps in the lower extremities and deep tenderness *without* objective signs. They resolve promptly with treatment. A diffuse polyneuritis of the Guillain Barré type sometimes occurs during the acute onset of ketosis in undiagnosed diabetes

Ischemic neuropathy is often present in adults with otherwise asymptomatic onset. These patients present pain paresthesias and cramps in the *lower extremities with areflexia and diminished vibratory sense perception*. A dramatic demonstration of the diagnostic importance of the latter abnormality was made by Collins with an electric vibrometer[18]. He picked up case after case of unsuspected diabetes among physicians attending a medical convention solely on the basis of vibratory preception impairment[8]

Visceral neuropathy may bring the patient to the urologist first because of atonic or hypotonic *bladder* symptoms

Impotence can be the presenting symptom of otherwise unrecognized diabetes. A young lieutenant paid no attention to the onset of moderate thirst and polyuria attributing it to the intense heat of summer and the large quantities of beer he imbibed as the army advanced through Germany in 1945. When sexual libido and potency vanished he promptly sought medical advice which led to the discovery of diabetes

Skin Manifestations — *Xanthosis* (*carotenemia*) an orange-yellow discoloration of the skin particularly of the palms and soles is commonly found in diabetes and therefore may be the physician s clue to the diagnosis as he first meets the patient

The prevailing assumption that diabetes predisposes an individual to *pyogenic* skin infections was not supported by the investigation of Williams[19] who found *no* difference in the incidence of boils and carbuncles between diabetic and non-diabetic patients among some forty thousand admissions into a general hospital

Renal Involvement —Some patients with a Kimmelstiel Wilson syndrome of diabetic glomerulosclerosis lack a history of diabetes and do not present glycosuria or fasting hyperglycemia. Leiter s coworkers[0] at the Montefiore Hospital point out the importance of performing glucose tolerance tests in patients with severe albuminuria finding impairment of the test as the only clue to the underlying diabetes in 7 per cent of patients with the full blown Kimmelstiel Wilson syndrome

Arteriosclerotic Manifestations —Premature arteriosclerosis of the coronary and peripheral vessels which characterize diabetes mellitus may be

presenting symptoms This accounts for the rather frequent discovery of unsuspected diabetes on the basis of such pathognomonic findings by the ophthalmologist optometrist, neurologist, cardiologist surgeon dentist and podiatrist[3]

Ocular Manifestations —*Refractive changes* occur in 2 to 6 per cent of patients at the onset of diabetes[4,6] The sudden onset of *myopia* usually arouses the oculist's suspicion of diabetes I recall the case of a young girl whose poor grades in school were found to be due to rapid changes in *refraction* which led to the discovery of otherwise unsuspected diabetes Temporary hypermetropia develops during the first days of diabetic treatment

The glucose content of aqueous humor is slightly less than that of plasma whereas that of vitreous humor is much lower[8] Since the aqueous humor content parallels the plasma glucose level more closely, it has been suggested that differences in the glucose content of the two chambers may account for rapid alterations in the refractive index[12] Hydration of the lens experimentally induces myopia by increasing the refractive index[9] but the mechanism whereby *hyperglycemia* can lead to the influx of water into that structure[10] is not understood In fact with hyperglycemia the alloxan diabetic dog develops hypermetropic, not myopic refractive changes[11]

The refractive changes may also be the cause of *headaches* which occur infrequently at this time

Lens changes are easily induced by hypertonicity due to any crystalloid[13] Temporary opacities have been noted in the lens during severe dehydration of diabetic and *nondiabetic* origin disappearing completely with rehydration[14] Despite lack of agreement as to the incidence of *cataracts* in diabetes most ophthalmologists consider the possibility of its existence when confronted by lenticular opacities This is justified since senile cataracts appear in the older age group in whom asymptomatic diabetes is especially prevalent

Diabetic retinopathy with or without subjective visual failure is not an infrequent casual finding in older patients in the course of routine ophthalmological examination Six per cent of patients in the fourth and fifth decades of life with asymptomatic diabetes had moderately advanced retinopathy[18] Some of them had no glycosuria whatsoever and normal or only slightly elevated fasting blood sugar levels were obtained but glucose tolerance curves were definitely impaired in all

I have also seen isolated instances of such ocular disturbances as *retrobulbar neuritis* *optic atrophy* and *central retinal vein thrombosis* as the presenting symptom of unsuspected diabetes an experience confirmed by others[4,15,16] The extremely high incidence of diabetes (8.4 per cent)[5] among the blind is a further indication of the close relationship between diabetes and ocular involvement

Dental Manifestations —It is interesting that John Rollo[17] in his classic treatise of 1797, the first rational attempt at the dietary treatment of diabetes noted the occurrence of certain dental changes as being a prominent physical finding His first patient one Captain Meredith presented gums which 'are reddish and have the appearance as influenced by mercury the teeth feel loose'

filtration rate and, therefore, a diminished tubular glucose load despite the existence of hyperglycemia

Normally the amount of glucose in the urine is so minute that the routine methods used for its determination give negative results Neither can glycosuria be detected after an oral glucose tolerance test in normal individuals On the other hand an extreme glycosuria of as much as 500 grams in twenty four hours has been obtained in diabetes [4]

Generally glycosuria parallels the course of the blood sugar being maximal after meals In severe untreated diabetes glycosuria and hyperglycemia continue to mount throughout the night This was formerly thought to be in contrast to mild ' cases where glycosuria subsided and disappeared during the night Recent investigations,[2] however, indicate a *diurnal rhythm* of hyperglycemia with lowest blood sugar levels (and decreasing glycosuria) in the late afternoon and evening and highest values in the early morning and forenoon in all types of diabetes, regardless of severity This accounts for the usual finding of maximal glycosuria after breakfast and in the forenoon in both mild and severe' cases with decreasing glycosuria toward the late afternoon Consequently, analysis of the urine two to three hours *after* the morning meal is the most desirable specimen for the detection of glycosuria

Glycosuria in severe diabetes is usually so constant that almost any urine specimen is likely to reveal it although exceptions occur frequently enough even in juvenile diabetes Because of this and the preponderance of mild diabetes generally a *postprandial urine is the specimen of choice* for *diagnostic* purposes in all cases

The detection of glucose depends upon reactions common to most other sugars and a number of non glucose reducing substances which may be present in the urine The tests include fermentation by yeast specific polariscopic rotation the production of typical osazone crystals and the reduction of metallic (copper or bismuth) oxides

Fermentation can readily be obtained from all the urinary sugars except the pentoses Lactose fermentation may vary according to the strain of yeast The test is performed by adding a small piece of baker s yeast to a fermentation tube filled with urine and permitting it to stand overnight at room temperature or preferably in an incubator at 37° C The amount of carbon dioxide gas formed in the closed arm of the tube indicates the per cent of fermentable sugar in the urine Persistence of a positive test with Benedict s solution after fermentation suggests the presence of pentose and possibly lacto e or galacto e

Polariscopic examination will differentiate fructose because of its unique levorotatory power but not glucose lactose galactose and sucrose which are all dextrorotatory Pentose is characterized by a complete lack of optical activity

Osazone crystal formation is rarely used in clinical practice because preparation and identification of specific crystals requires confirmation by specific melting point determinations Characteristic osazones are formed by glucose and pentose with phenylhydrazine and by fructose with methyl phenylhydrazine

clinically so *disproportionate* to the symptoms of the metabolic disorder as to obscure the nature of the *underlying* disease. The incidence of fatal coronary disease among diabetic *men and women* is *twice* that of non-diabetic males and *triple* that of non-diabetic females respectively.[1] Therefore, suspicion of asymptomatic diabetes should be aroused in every case of *coronary artery disease* particularly in *women* since they normally present an incidence of such cardiovascular involvement only about half as frequently as men.

The diabetic predisposition to *peripheral vascular disease* is even more striking. Bell[22] claims that on the basis of arteriosclerosis alone, *gangrene* develops nearly 40 times more frequently in diabetic than in non-diabetic individuals. As with coronary artery disease diabetes obliterates the normal sex differences of masculine predominance in peripheral arteriosclerosis, the frequency in both sexes being equal when diabetes is present. Therefore the appearance of symptoms or signs of peripheral vascular disease should stimulate an investigation for asymptomatic diabetes.

The *importance* of the *clinical* diagnosis of diabetes has been emphasized because for *practical purposes* its detection cannot be relied upon laboratory determinations of urine and blood sugar alone. The degenerative manifestations of diabetes which have been described above are so varied and so *protean* that this disease now surpasses syphilis as "the Great Imitator."

LABORATORY DIAGNOSIS

The finding of "*sugar*" in the urine, historically the oldest, and clinically the *simplest diagnostic* test for diabetes mellitus, is first noted in the course of *examination for* some *other* purpose in almost one half the patients. A *surprising* medical inertia still exists towards more frequent analysis *for glycosuria in the* absence of gross symptoms. This is corroborated by Joslin's survey among the *inhabitants* of *Arizona* who had enjoyed the lowest incidence of diabetes until by *the simple* expedient of routine urinalysis a frequency no different from that of Rhode Island was revealed.[23] A few patients suspect the diagnosis and present themselves to a physician with the fact already established by a positive laboratory finding of "sugar in the urine." I know of only 1 patient who resorted to the ancient *technic of tasting the urine*. *She offered little objection* when a more modern procedure was suggested, except for a muttered comment that it could not be as simple or as cheap!

Glycosuria.—The mechanism of glycosuria described on page 940 indicates the relation of the urinary excretion of glucose to the level of hyperglycemia, and the rates of renal glomerular filtration and tubular reabsorption. The *renal threshold* represents an artificial concept subject to wide variations, the usually accepted range lying between 140 to 200 mg per 100 cc of blood sugar concentration. A "high threshold" is not uncommon in diabetes, especially as the duration of the disease increases the degree of associated vascular damage. It is also characteristic of older diabetic patients, regardless of duration. Degenerative disease of the renal arteries, arterioles, and glomeruli results in *decreased* renal blood flow and

Galatest (Denver Chemical Mfg Co Inc New York N Y) depends upon the reduction of a bismuth salt It is performed very simply and most *rapidly* by the addition of 1 drop of urine to a small amount of Galatest reagent (about the size of a large pinch of salt) on any white surface paper porcelain etc The result is read after thirty seconds according to grada tions of color from gray to black with increasing concentrations of sugar A color chart also accompanies this reagent but quantitation is not as satisfactory as with Clinitest

Nonglucose Urinary Sugars — A pronounced reduction is also obtained in *nondiabetic glycosuria*, the most significant of which include the nonglucose sugars fructose pentose lactose and galactose and the conditions renal glycosuria alimentary hyperglycemia and "emotional" or "stress" glycosuria

Fructosuria and *galactosuria* are extremely rare congenital metabolic anomalies with defects in enzymatic interconversion to glucose as described on page 933 *Pentosuria* and *renal glycosuria* are somewhat more frequent "inborn errors of metabolism" These 4 conditions represent fixed disorders which persist throughout life and except for galactosemia are *asymptomatic* Coincidental association with diabetes mellitus has been reported in cases of fructosuria pentosuria and renal glycosuria

Fructosuria —*Fructosuria* (levulosuria) appears only after the ingestion of food containing fructose or sucrose (fruit, honey and cane sugar) and disappears in the post absorptive or fasting state The fructose is excreted in a fixed proportion of about 14 per cent of the intake According to Silver and Reiner [6] a reciprocal relation develops between the fructose and glucose content of blood following administration of fructose to patients with this defect As with galactosemia (page 933) *the blood glucose* level falls as its fructose content rises and then returns to normal as the fructose disappears in being metabolized and excreted They also demonstrated the insignificant effect of insulin and epinephrine on fructose metabolism This has now been proven directly by the observation of a normal fructose tolerance in the untreated depancreatized dog [27] Fructosuria *and* pentosuria are Mendelian recessive hereditary characters being common in siblings and absent *in their parents and children* [3] *Neither condition* is peculiar to any one national or racial group age or sex [28]

The *diagnosis* of essential fructosuria can be established by the following reactions of the sugar found in the urine

1 Positive *reduction* of *Benedict s* Solution (a) *at room temperature* within a few hours or (b) at 55° C within ten minutes This response is *also* obtained with *pentosuria* The test is performed using 1 cc of urine added to 5 cc of Benedict s qualitative reagent
2 Specific *levorotation* on *polariscopy* which *disappears* after fermentation
3 Specific *osazone* crystal formation with methylphenylhydrazine having a melting point of 153° C
4 Positive *Seliwanoff* test Equal quantities of urine and 25 per cent hydrochloric acid are brought to a boil in a test tube over a free flame A few crystals of resorcinol are added and boiling is continued for only ten seconds In the presence of fructose the solution turns *red* and a reddish brown precipitate forms which is soluble in alcohol

Copper oxide reduction tests employed in Benedict's qualitative reagent and others are the most widely used routine methods for the detection of sugar in the urine. Sucrose is the only non reducing sugar. The alkaline copper solution is reduced with the formation of a green, yellow or red colloidal precipitate if more than 0.2 to 0.3 per cent of sugar is present. With smaller amounts of sugar the precipitate will appear only on cooling.

Benedict's qualitative test is performed by adding 8 drops of urine to 5 cc (average teaspoonful) of the qualitative (*not* the quantitative) reagent, mixing thoroughly by shaking and heating either in boiling water for five minutes or over a free flame for one to two minutes (with the solution boiling all this time). Allow for spontaneous cooling before judging the result. If no sugar is present or if it amounts to less than 0.1 per cent the solution will remain unchanged from its original clear blue color. Estimation of the quantity may be made on the basis of the color as follows:

Blue-green	0.1%
Yellow green	0.5%
Yellow	1.0%
Brown or red	over 2.0%

False negative tests result from incomplete copper reduction when *insufficient time* is given to the heating of Fehling's or Benedict's solutions. This cannot happen with the commercial preparations Galatest and Clinitest. Creatinine and sulfanilamide will mask traces of glycosuria and give negative tests.

False positive tests with only slight reduction are usually due to conjugated glycuronates which appear only after the administration of drugs such as salicylates, amidopyrine, chloral hydrate, neocincophen, etc. Since these are decomposition products their interference can be overcome by using *freshly voided* urine specimens. Urates produce a faint turbidity or reduction which can be overcome by repeating the test after filtering off the urate precipitate which is formed when the specimen is kept in an ice box for several hours. Benedict's solution is less susceptible than Fehling's to false reduction.

Two commercial preparations, Clinitest and Galatest, based on metallic oxide reduction methods are much more convenient and much less time-consuming than Benedict's test for office and clinic practice. Their simplicity and rapidity make them more suitable for use by patients.

Clinitest (Ames Co., Inc., Elkhart, Ind.) requires a particular size dropper and test tube as supplied in the original outfit if reproducible standardized results are to be obtained. Ten drops of tap water are placed in the tube to which 5 drops of urine are then added. One Clinitest reagent tablet is added to this and its heat of solution produces boiling spontaneously. The tube should not be shaken during boiling lest the layer of carbon dioxide evolved, which overlies the solution, be broken up, resulting in aerobic interference with reduction. The colors appearing within several seconds of the completion of boiling are similar to those obtained with Benedict's solution described above. A card depicting the various colors and their interpretation accompanies each outfit and permits fairly satisfactory quantitation for practical purposes.

6 *Aniline acetate test* This is obtained by heating equal quantities of the urine and concentrated hydrochloric acid and holding a strip of filter paper dipped in aniline acetate (aniline oil + acetic acid) in the fumes of the upper part of the test tube A cherry red color denotes pentose by its formation of furfural

7 Characteristic *osa one* with a specific melting point (158° C) formed with phenylhydrazine

Instances of diabetes mellitus developing in patients with chronic essential pentosuria have been reported[35] The constancy of the urinary excretion of pentose makes it most liable to misinterpretation as indicating diabetes mellitus A report[36] of the production of 'diabetic symptoms' polyuria and thirst by pentosuria does not seem valid since the mechanism of polyuria cannot be induced by the small amount of urinary pentose

Lactosuria — The hyperglycemia of diabetic lactating women does not alter the lactose content of the milk nor enable glucose itself to enter the milk[32] Glucose not lactose is the characteristic urinary sugar for the greater part of pregnancy It appears as a result of a transient *renal glycosuria* which is fairly common during pregnancy *Lactosuria* a physiologic event appears only at the *end* of pregnancy, a marked increase developing two to three days antepartum with the maximal level being reached at the time of delivery Immediately postpartum lactosuria drops to a low level for several days and then abruptly increases often tremendously with fluctuations for about one month Thereafter it declines to a lower constant level and disappears completely after weaning[33]

The *diagnosis* of lactosuria depends primarily upon clinical awareness of the existence of lactation Lactose reduces Benedict s and other copper solutions to the same degree as glucose and has about the same polariscopic effect It can be distinguished by the following

1 *Lack of fermentation* ordinarily Certain strains of bakers yeast however yield a *slow* fermentation After a period of fermentation usually adequate to remove glucose completely, persistence of polariscopic dextrorotation suggests the presence of lactose

2 Positive *Methylamine test*[34] To 5 cc of urine add 1 cc of an aqueous solution of methylamine hydrochloride (0 2 per cent) and 0 2 cc of sodium hydroxide (10 per cent) Mix by gentle swirling or inversion Cover the test tube with a glass ball or marble and place it in a water bath at 56° C for thirty minutes At the end of this period remove the tube from the bath and allow it to stand at room temperature If a large amount of lactose is present a *red* color will appear before the heating is over and will increase further on standing reaching a *maximum in about one hour* At *room temperature* an intense red color appears in fifteen to twenty minutes when 0 5 per cent lactose is present and a slight but definite red color appears in thirty minutes with 0 05 per cent Aeration which must be avoided is minimized by gentle mixing and covering the tube during heating Maltose is the only other sugar which produces a similar red color All the others including pentose sucrose glucose fructose and galactose give a yellow color

5 *Lasker's clinical test*[30] A supper of meat or fish, white bread and milk or coffee or tea is permitted the night before. Fruits, vegetables, salads, sugar and sweets are forbidden since they contain fructose. Breakfast the next day consists of milk or coffee *without* sugar. Following this a urine specimen is obtained and 50 grams of *glucose* in water is given orally. A second urine specimen is collected one and one half hours later. The same procedure is repeated the next day substituting 50 grams of *sucrose* instead of the glucose and 2 urine specimens are obtained as before. The diagnosis of essential fructosuria is quickly evident simply by examination of the urine with Benedict's reagent for glucose, positive reduction being obtained in the last specimen only, the first three remaining negative. This response to fructose deprivation and load is simple, specific and extremely practical.

Since fructose is as readily fermentable as glucose this procedure is of no value in differentiation.

Essential Pentosuria — *Essential Pentosuria* (xylulosuria) is of no clinical significance since the 5-carbon sugar excreted in the urine is related to glucuronic acid[32] and not to the tissue pentoses, ribose and desoxyribose. The urinary excretion of pentose is relatively small (2 to 4 grams daily), continuous and *unrelated* to the diet. It remains constant for each person. This contrasts with alimentary pentosuria wherein transient excretion of pentose into the urine follows the ingestion of certain fruits (cherries, plums, prunes and berries), wine and beer. The hereditary aspects of essential pentosuria have been described above.

The *diagnosis* of essential pentosuria is based on the following reactions of the reducing substance found in the urine:

1 Lack of *fermentation*
2 Optical *inactivity* on *polariscopy*
3 Positive rapid *reduction* of *Benedict's* reagent *at room temperature* or 55° C. as with fructose (see above). Furthermore a urine containing pentose will retain its reducing power almost *indefinitely* whereas glucose will disappear in one or two days due to glycolysis.
4 Positive *Bial test*. The reagent consists of orcinol 1.5 gm., fuming hydrochloric acid 500 gm. and 20 to 30 drops of 10 per cent ferric chloride. The test is performed by gentle heating of the test tube containing 5 cc. of the reagent and 3 cc. of urine. A *green* color appears, often accompanied by a flocculent green precipitate at the first sign of boiling or upon cooling.
A false positive test may result in the presence of glucoronates or galactose. The former may be removed by treating the urine with Merck's blood charcoal. Interference by glucuronates can also be prevented by using freshly voided urine and by avoiding prolonged boiling. Galactose does not yield any spectroscopic absorption bands after Bial's test whereas pentose gives a typical one between lines C and D.
5 Positive *Benzidine test*[31]. This is performed by vigorously boiling 0.1 cc. urine and 0.5 cc. benzidine solution (1.0 gm. benzidine in 25 cc. glacial acetic acid). The mixture is cooled under tap water and 1 cc. distilled water is added. A *pink* to *red* color appears immediately in the presence of pentose, in its absence the mixture is yellowish brown.

hyperglycemia is also often associated with it[38] Unlike lactosuria which is a physiologic terminal event of pregnancy glucose may be found in the urine at any trimester of gestation and disappears with parturition So common is its appearance (about 14 per cent) that it had been suggested as a diagnostic sign of pregnancy[38] The transitory lowering of the renal threshold during pregnancy might be considered in ACTH or anterior pituitary effect particularly since the mothers with *nondiabetic* glycosuria often give birth to oversized infants with splanchnomegaly[?] In fact the pioneer observations of Miller and his coworkers[40] concluded that the benign glycosuria of pregnancy is not benign for the fetus The offspring of these women showed the same changes and the same poor survival rate as did those born to mothers with frank diabetes mellitus Obviously innocent glycosuria appearing during pregnancy does not warrant treatment but deserves periodic observation for the rest of the woman s life

Alimentary Hyperglycemia and Glycosuria.—The disposition of the hyperglycemia which normally follows the ingestion of glucose and other rapidly absorbed carbohydrates depends mainly on the capacity of the liver to deposit it as glycogen and to a very minor extent on utilization by the peripheral tissue Ordinarily the hepatic mechanism for the homeostatic regulation of the blood sugar is more than equal to any amount of glucose which can be presented to it physiologically *Pijoan and Gibson*[41] found this capacity sufficiently adequate to remove 87 5 per cent of intravenously administered glucose from the circulating plasma within four *minutes* from the time of injection From 30 to 50 grams of glucose suffice to produce maximum hyperglycemia *ordinarily* increasing the amount administered only prolongs the duration of hyperglycemia without influencing its degree[42] Within twenty to thirty minutes after the ingestion of glucose its arterial blood level has reached the maximum level usually between 150 to 220 mg per cent

It is apparent that acceleration of intestinal absorption as seen after gastrectomy in hyperthyroidism and in states of increased gastrointestinal motility may produce alimentary hyperglycemia and glycosuria A diminished capacity for rapid glucose deposition in the liver is the cause of transitory glycosuria which follows carbohydrate ingestion in starvation diabetes states of carbohydrate deprivation and diseases of the liver The same phenomenon may occur during any acute illness febrile condition hyperthyroidism pregnancy etc A large variety of possible predisposing conditions accounts for the high frequency of this transitory form of glycosuria

The *diagnosis* can be established only on the basis of a glucose tolerance test with particular attention to capillary blood sugar determinations obtained at ten minute intervals within the initial half hour period An extreme hyperglycemia capable of producing glycosuria may be evident only at this time the subsequent curve lying within normal limits

Emotional Glycosuria—The classic frequent finding of mild transitory glycosuria in students undergoing examinations is often mentioned in discussions on emotional glycosuria No evidence has ever been presented of the existence of emotional *hyperglycemia in man* Therefore the phenomenon probably represents the result of an increased glomerular

3 Positive *mucic acid test* This denotes *either* lactose or galactose but the latter can be excluded by the methylamine test above Initially 5 to 10 cc of urine must be concentrated down to about 1 cc To it 1 cc of concentrated nitric acid is then added and heated in boiling water for one and one-half hours This is followed by the addition of 1 cc of water and the solution is permitted to stand overnight A crystalline insoluble gritty precipitate of mucic acid develops

4 *Positive Rubner test* This test is performed by adding 2 grams of lead acetate to 10 cc of urine shaking well and then filtering The filtrate *is boiled briefly, 1 to 2 cc of strong ammonia is added and the mixture* is reheated In the presence of lactose the solution turns brick red and a *red precipitate* is formed Although glucose also yields a red solution its precipitate is yellow

Galactosuria and galactosemia a rare congenital defect, usually limited to infants and children has been described on page 933 The clinical picture of galactosuria albuminuria lack of growth and development, cataracts and hepatomegaly is strikingly characteristic Although a positive mucic acid test is also obtained from lactose the latter can be excluded on the basis of a negative methylamine test when galactose is present

Sucrosuria is extremely rare and of no clinical significance Since it does *not* reduce Benedict s solution it can only be suspected because of the extremely high specific gravity of the urine, up to 1 070

Benign Glycosuria —Far more common than nonglucose melituria is glycosuria of nondiabetic origin including renal glycosuria alimentary glycosuria and the transitory glycosuria associated with states of "stress" such as emotional disturbances infections trauma etc The incidence varies from 10 to 14 per cent of any large series of examinations for glycosuria[6] with renal glycosuria being least significant statistically The importance of alimentary and the transitory forms of glycosuria lies in the fact that 10 *per cent* of these patients eventually develop diabetes mellitus[6] indicating some premonitory value in apparently benign glycosuria

Renal Glycosuria —True renal glycosuria represents a defect specifically limited to the tubular reabsorption of glucose probably in its phosphorylation mechanism Other tubular functions such as diodrast clearance and ascorbic acid resorption are perfectly normal in these patients[37] Glycosuria appears with blood sugar levels as low as 100 and even 50 mg per cent making it continuous and independent of the diet In milder instances glycosuria may not appear until almost normoglycemic levels are reached Once the urinary sugar has been identified as glucose the diagnosis is easily established on obtaining a normal glucose tolerance curve Even with marked glycosuria (up to 50 grams or more daily) the condition remains asymptomatic resembling that of many diabetic patients in whom glycosuria is *not* associated with polyuria Carbohydrate restriction serves no useful purpose and provokes acetonuria if pushed to an extreme because of an erroneous diagnosis as diabetes mellitus It should be noted in passing that glycosuria may be a manifestation of renal tubular disease (nephrosis Fanconi syndrome)

Glycosuria of pregnancy deserves particular mention here since its mechanism is predominantly that of a renal glycosuria[38,40] although alimentary

nation revealed glycosuria The symptoms and glycosuria had subsided without treatment when the first blood sugar determination was made and a fasting value of 100 mg per cent reported This was repeated one month later and a level of 110 mg per cent was obtained An oral glucose tolerance test indicated the existence of diabetes according to the following data

Time in hours	*Fasting*	½	*1*	*2*	*3*
Blood sugar in mg per cent	110	230	310	275	210
Glycosuria	0	0	3 3%	2 3%	1%

Two weeks later glycosuria and hyperglycemia were noted in the fasting specimens

As in the case of glycosuria, the diagnostic value of the *fasting* or postabsorptive blood sugar level is often *limited* A normal value either for urine or blood sugar does not exclude the existence of diabetes The probability of finding apparently normal fasting blood sugar levels in suspected diabetes is enhanced in the absence of glycosuria Consequently the patient must be subjected to a *confirmatory* procedure which may consist either of a standard *glucose tolerance test* or much simpler an *isolated blood sugar* determination obtained two to two and one-half hours *after a normal meal* The latter procedure now standard practice in the routine detection of diabetes is extremely practical for *office* use the existence of diabetes being suggested by a value at that time of over 140 mg per cent Not only is the physician assured of a greater probability in obtaining a positive diagnosis but the patient is spared the nuisance of repeated, confirmatory tests Good correlation has been obtained between the two hour postprandial blood sugar level and the standard oral and intravenous glucose tolerance tests[66]

A *fasting* blood sugar determination for diagnostic purposes should be *limited* to instances of frank *glycosuria* at that time In such cases hyperglycemia will be found if diabetes is present and nondiabetic glycosuria will be suspected if normoglycemia obtains

Variations in blood sugar determinations due to different technics must be considered in evaluating the result The traditional methods for macro- (Folin Wu) and micro- (Folin Malmros) determinations depend on the reduction of potassium ferricyanide by glucose to ferrocyanide and conversion of the latter to Prussian blue on the addition of a ferric salt This test and its modifications yield results somewhat higher than the true glucose content because blood contains a number of *nonglucose reducing* substances These consist mainly of glutathione cysteine ergothionine and creatinine in a total concentration of about 30 mg per cent ordinarily Marked variations in their content from 1 to 78 mg per cent have been reported not only in different individuals but also in the same individual during the course of a glucose tolerance test[48] *Tungstic acid* does not precipitate non glucose reducing substances along with the blood proteins in the first step of the Folin methods Since the *zinc hydroxide* precipitation of blood proteins (Somogyi modification[49]) removes these interfering substances as well as the anticoagulants a true blood sugar value is obtained and this technic has become the basis of the newer methods of blood sugar determination

filtration rate accompanying the generally increased blood flow during excitement which exceeds the capacity for the tubular reabsorption of glucose.[42]

Glycosuria During Stress, Anoxia or Shock.—Overwhelming infections associated with shock, such as acute meningococcic meningitis,[43] and tissue anoxia resulting from a prolonged state of shock or collapse[44] as in acute coronary thrombosis[45] not infrequently are accompanied by glycosuria. Frequently associated with hyperglycemia and glycosuria in these states is hepatic damage demonstrated pathologically by the finding of centrilobular necrosis in the liver during anoxia[44] and following cardiac infarction.[45, 46] It seems likely that the elevation in the blood sugar level is related to the outpouring of adrenocortical glycogenic steroids in these states.

Recognition of this nondiabetic type of glycosuria is extremely important. The onset of meningitis with coma, glycosuria and acetonuria, (the latter due to hepatic glycogen depletion) may mask the meningeal signs and lead to a diagnosis of diabetic acidosis resulting in a *fatal delay* in the initiation of proper treatment for the underlying disease.[43, 47] Similarly patients with acute coronary occlusion have been treated unnecessarily for diabetes or diabetic acidosis to the point of fatal hypoglycemia.

Illustrative Case

A sixty year old woman in apparent good health had gone out into the country to pick berries. She suddenly felt ill, vomited several times and collapsed in the field. When brought to the hospital several hours later in a state of shock, examination of the urine revealed a 1+ glycosuria and 3+ acetonuria. One hundred units of regular (unmodified) insulin was administered promptly, followed by 1000 cc. of normal saline solution intravenously. Collapse became more intense, anuria set in and death occurred within twelve hours. A blood sugar value of 10 mg. per cent was obtained just before death. Postmortem examination revealed a typical acute coronary thrombosis with infarction.

Summary.—*Nondiabetic glycosuria* and melituria due to sugars other than glucose comprise about 15 per cent of all cases *originally suspected as diabetes mellitus.*[6] The latter eventually develops in about 10 per cent of the entire nondiabetic group parallel with advancing age, and appearing in a mild form in most instances.[6] Frequently treated as diabetes mellitus at first, the nondiabetic origin of the urinary findings is usually first discovered because of the *absence of hyperglycemia*. Then *identification* of the particular *sugar* is established. A *glucose tolerance test* is necessary for the correct diagnosis in the cases where *glucose* proves to be the urinary sugar.

Diagnostic Value of Hyperglycemia.—An elevated fasting blood sugar level may be found in a variety of acute conditions as described above *without* implying the existence of diabetes. On the other hand, a *normal* fasting value is not uncommon in diabetes, being found in 21 per cent of "mild" cases at the Mayo Clinic.[50] Although this is a fairly well recognized finding among older patients, it also appears in juvenile diabetes as indicated by the following case history.

Illustrative Case

A fifteen year old girl with a marked familial history of diabetes developed symptoms of excessive thirst, polyuria and asthenia. A routine school exami-

In normal individuals consecutive repetition of an intravenous glucose tolerance test at end of every two hour period results in progressively lower curves,[52] a phenomenon also observed in untreated diabetic patients.[6]

In the light of the preceding discussion it is obvious that the glucose tolerance must be viewed as an unphysiologic "load" which acts more as a measure of liver function than of the organism's capacity to utilize glucose. Only if the many conditions capable of influencing the test are excluded and standard basal conditions can be obtained preparatory to and during the procedure may valid deductions be obtained from a glucose tolerance test. Even so, reproducibility of results is not easily secured with this inherently variable diagnostic procedure.

Although carbohydrate restriction should be avoided preliminary to the test, it is *not* necessary that a standard preparatory diet of 300 grams of carbohydrate be employed three to five days beforehand.[63] Sweeney, who first noted the influence of this factor on the test,[52] believes that 20 to 35 grams daily is sufficient to insure normal conditions.[64] For practical purposes, therefore, the patient need only continue his usual diet, being cautioned solely against any attempt at "starvation" or fasting.

Standard Oral Glucose Tolerance Test.—Method.—The subject reports without breakfast and fasting blood samples (either venous, from the arm, or capillary, from the finger) and urine specimens are obtained for determinations of the sugar content. One hundred grams of glucose dissolved *in about 300 cc or 2 glassfuls of water is flavored with lemon juice* and administered orally. An equally satisfactory amount of glucose, 1.75 grams per kilogram of body weight, is often used. The latter dose is more easily tolerated by children and many adults. Infants under two years *require a larger dose in order to evoke the maximal response*, 3 grams per kilogram of body weight being suggested.[65]

Specimens of blood and urine are obtained at intervals of one-half hour, one, two and three hours after the ingestion of glucose. Capillary blood sugar values will exceed those *of venous blood by 20 to 70 mg per cent* at the peak rise, but the two approach each other closely at the beginning and end of the test. This provides the only discrepancy in results between the two sources of blood. Allowance must also be made for lower overall values when methods which exclude interference by nonglucose-reducing substances are used.

Diagnostic Criteria.—1. Since the *initial fasting level* of the blood sugar may be normal in 21 per cent of patients with mild diabetes,[50] it constitutes the *least important* criterion in the diagnosis. This does not minimize the importance of a finding of definite *initial hyperglycemia* as corroboration of the diagnosis *per se*.

2. The significance of the *height* of the curve is disputed. Joslin[6] regards any capillary blood sugar value of over 200 mg per cent as justifying a diagnosis of diabetes, while most other observers[64,6] ignore it.

3. It is generally agreed that the test's most *important criterion for the diagnosis of diabetes* is the *duration* of hyperglycemia, i.e., the *rate of return* of the blood sugar level to its original normal value by the second to third hour. The former hour obtains for venous and the latter for capillary

The *normal* fasting blood sugar level ranges from 80 to 120 mg per cent by the Folin methods and between 60 to 100 mg per cent when the Somogyi or similar modifications of filtrate preparation are used

Either *capillary* or *venous* blood sugar determinations can be used for *diagnostic* purposes, their values being clinically comparable During fasting or in the postabsorptive state the two are almost identical, diverging markedly only at the peak of a glucose tolerance test, when the capillary blood sugar levels tend to be higher than the venous by 30 to 70 mg per cent Two hours after the ingestion of glucose when the capillary value has returned to the *original* level the venous blood sugar content is usually still somewhat lower No practical purpose is served by an analysis of the arteriovenous (A V) blood sugar differences

The degree of hyperglycemia cannot be used as an index of the severity of diabetes or as a basis for the type of treatment required Extremely high values (*e g* 400 mg per cent) may be found in patients with but few symptoms, and who may respond satisfactorily to simple dietary restriction without the use of insulin In severe untreated diabetic acidosis on the other hand malnutrition and carbohydrate store depletion may be so extreme as to cause only moderate hyperglycemia (*e g* 200 mg per cent)

Glucose Tolerance Tests — A finding of *glycosuria and hyperglycemia* in the fasting state is sufficient evidence of diabetes in itself without further resort to a totally *unnecessary* glucose tolerance test The latter should be reserved for the diagnosis of

1) *Diabetes* suggested by glycosuria and/or hyperglycemia in the two hour postprandial period in the *absence* of these positive findings on fasting

2) *Nondiabetic glycosuria* suggested by glycosuria either on fasting or postprandially associated with *normoglycemia* at either time

Is impairment of glucose tolerance synonymous with diabetes mellitus — A negative answer to this question is the only possible one in the light of the following discussion Elevation of the blood sugar level due to causes other than diabetes has been discussed and demonstrated as being limited in frequency Disturbances in glucose tolerance however are often evident as a result of many varied commonly occurring conditions An abnormal diabetic curve may be found in malnutrition [51] carbohydrate restriction [52] toxemia [61] liver disease [53] alcoholism [54] advancing age [55] physical inactivity [56] rheumatoid arthritis [57] intracranial injury [58] and hyperfunction of the thyroid pituitary and adrenal glands etc Such abnormal curves do not remain static but fluctuate widely within the same individual during the course of any of the above conditions

Furthermore *remissions* of diabetes occurring spontaneously or more frequently following removal of a precipitating factor as in the case of other endocrine disorders infections and trauma are characterized by a perfectly *normal* glucose tolerance But good clinical judgment demands that such cases be regarded as having diabetes albeit in latent or potential ' form Restoration to a normal response to glucose is frequently possible for the obese mild diabetic following reduction in weight [59] In fact the administration of a high carbohydrate diet to the non-obese mild diabetic may also lead to a normal test [60]

In normal individuals, consecutive repetition of an intravenous glucose tolerance test at end of every two hour period results in progressively lower curves,[63] a phenomenon also observed in untreated diabetic patients.[4]

In the light of the preceding discussion it is obvious that the glucose tolerance must be viewed as an unphysiologic "load" which acts more as a measure of liver function than of the organism's capacity to utilize glucose. Only if the many conditions capable of influencing the test are excluded and standard basal conditions can be obtained preparatory to and during the procedure may valid deductions be obtained from a glucose tolerance test. Even so, reproducibility of results is not easily secured with this inherently variable diagnostic procedure.

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blood Hepatic damage is the only common condition other than diabetes wherein *hyperglycemic levels* persist *beyond* the *third* hour

When *all* 3 criteria satisfy the diagnosis of diabetes mellitus the test has been superfluous In this case, sufficient evidence must have been present in the hyperglycemia *and* glycosuria of either the fasting or two hour postprandial state The glucose tolerance test is most useful in the "borderline case" in whom the *third* criterion *alone*, abnormal prolongation of an elevated blood sugar level suffices to confirm the diagnosis of diabetes

One Hour Two Dose Glucose Tolerance Test (Exton Rose[65]) — This test is carried out by giving two 50 gram doses of glucose 30 minutes apart and determining the blood and urine sugar content at 0 30 and 60 minutes

Diagnostic Criteria — A normal response includes

1 A fasting blood sugar level within the normal limits of the method employed
2 A rise in blood sugar level in the thirty minute sample not exceeding 75 mg per cent
3 A blood sugar value in the sixty minute sample either less than or the same as that of the thirty minute sample
4 All urine specimens remain negative to Benedict s test

The Exton Rose procedure became extremely popular because of its brevity and the few laboratory determinations which it entailed Careful investigation however has proven it markedly *inaccurate* yielding a prohibitive number of *false positive* results in normal individuals[66] Furthermore the second 50 gram dose of glucose is unnecessary and *not* responsible at all for the second half of the curve since *more* than 50 grams of glucose can be *recovered* from the stomach at the end of one hour[69 70]

Intravenous Glucose Tolerance Test —In order to overcome the variable factor of intestinal absorption intravenous glucose tolerance tests have been devised As with the oral route no standard method has found universal acceptance but the following 3 forms of the test have been proposed

1 *Lozner* and his associates[1] administer 25 grams of glucose (as 50 cc of a 50 per cent solution) intravenously within a two minute period after a fasting blood specimen is obtained No correction in the dose is made for the age size or sex of the patient A second and final blood specimen is obtained at the end of two hours

The response is considered normal when both the *initial* and *terminal* capillary blood sugar values are under 120 mg per cent In diabetes mellitus, higher initial readings are obtained as often as fasting hyperglycemia occurs in this condition but *terminal* elevations *above* 120 mg per cent are quite specific Malnutrition occasionally yields abnormally high terminal values[71] and infrequently a normal test may be found in a proven case of diabetes[66] This test is somewhat *less sensitive* than the oral procedure in that borderline diabetes often eludes detection by it[66]

2 *Soskin and Levine s*[63] modification consists in the use of one-third of a gram of glucose per kilogram of body weight administered in an aqueous (50 per cent) solution which is injected intravenously within three to five

minutes Samples of capillary blood are drawn just prior to the injection and at one-half one and two hour intervals thereafter

In *normal* individuals the blood sugar level returns to the *initial* value within *one hour* while in *diabetes at least two hours* is required for this effect In liver disease, the return *to* preinjection levels is achieved between one to two hours in 75 per cent of cases and within the first hour in 25 per cent

3 *Thorn* and his coworkers[73] developed the following modification One-half gram of glucose per kilogram of body weight is administered as a 20 per cent *solution by the intravenous route over a thirty minute period* The latter *proviso* makes for a more physiologic injection it is claimed since it equals the average rate of intestinal absorption of glucose in man Venous *blood* samples are drawn in the fasting state and at half hour intervals for three hours

The chief criterion for a *normal* response is the *return* of the blood sugar level to that of the fasting period *within two to two and one half hours* after the beginning of the glucose infusion The height reached at the peak of the curve is of no importance while the fasting blood sugar level retains its significance independent of the test being considered abnormal if over 120 mg per cent This test is obviously not suitable for office or clinic practice

4 *Forsham and Thorn*[2] propose an unusual refinement of the intravenous glucose tolerance test as an aid in the diagnosis of early diabetes mellitus by a study of concurrent changes in *serum inorganic phosphorus* A maximum fall in the latter level occurs between one and one-half and two hours after the beginning of the glucose infusion In diabetes this may be reduced to only 12 per cent of the initial serum inorganic phosphorus level (average normal maximum fall 25 per cent) The value of this test has *not* been established Abundant evidence indicates that the fall in serum inorganic phosphorus is *not* related to the effect of insulin[27, 4]

Concluding Remarks on the Value of Glucose Tolerance Tests — A single blood sugar determination limited to the two hour postprandial period provides as much diagnostic information with regard to the existence of diabetes mellitus as can be obtained from all the more elaborate glucose tolerance tests with but rare exception[66]

The Basis for the Diagnosis of Diabetes Mellitus in Summary —

I If the patient presents *any* of the classical *symptoms* along with *glycosuria* the diagnosis needs but a single confirmatory determination *i e* the finding of an *abnormal elevation* of the blood sugar level in the *fasting state* *Glycosuria* at this time although expected is *not* necessary for the diagnosis in the presence of fasting hyperglycemia

II If *symptoms* are *lacking* but *glycosuria* is found incidentally in a *random* specimen the suspected diagnosis may be confirmed by obtaining the following data

a An abnormal *elevation* of the blood sugar level in the *fasting state* when *glycosuria* is found in the *pre-breakfast* specimen A normal blood sugar level concomitant with glycosuria in the fasting state indicates nondiabetic or benign glycosuria In *this* instance a glucose tolerance test and identification of the urinary sugar are essential to the diagnosis

b *Hyperglycemia* in the *two hour postprandial* specimen if *glycosuria* is *absent* in the fasting state This will obviate the need for a time consuming glucose tolerance test except in the case of "borderline or doubtful" hyperglycemic values The simultaneous appearance of glycosuria with normal blood sugar values in the two hour postprandial specimen suggests non diabetic or benign glycosuria A glucose tolerance test and identification of the urinary sugar are required for the diagnosis in this instance

c An abnormal *glucose tolerance test* This procedure should be resorted to only because of

1 *borderline hyperglycemic* values in either II*a* or II*b* suggestive of diabetes *e g* between 120 and 140 gm per cent by the Folin Wu method

2 *Glycosuria* in the presence of *normoglycemia* in either II*a* or II*b* suggestive of nondiabetic or benign glycosuria

The *clinical* diagnosis of diabetes is equally as *important* as its *chemical confirmation* Glycosuria hyperglycemia or impaired glucose tolerance cannot "make" the diagnosis alone they can only be used to corroborate it Failure to integrate the chemical data with the clinical manifestations leads to *erroneous diagnosis* and *treatment*

False stigmatization of normal individuals as diabetic subjects them to unnecessary treatment and anxiety and jeopardizes their insurability These victims account for almost 15 per cent of all patients *seeking treatment* at Joslin s clinic [6]

I vividly recall the tragic case of a young woman who suffered great physical and psychic trauma as a consequence of such a mistake In addition to disfigurement from severe atrophy of the skin of the thighs due to unnecessary insulin injections for many years she had been doomed to barrenness because of a needless hysterectomy Although only a small fibroid was found on laparotomy the uterus was removed on the archaic assumption that any future pregnancy would be contraindicated because of the "diabetes" This finally proved to be nothing but simple renal glycosuria when a glucose tolerance test was belatedly performed for the first time

In the absence of glycosuria and related symptoms the physician may ignore clinical evidences of diabetes and erroneously dismiss a *bona fide* case of disease as normal The diagnosis of diabetes may never be established definitively in some borderline incipient potential cases in whom mild abnormalities of carbohydrate metabolism persist without progression for many years

The physician cannot delegate the responsibility for the diagnosis of diabetes mellitus to a laboratory on the basis of a few drops of blood or urine A very important adjuvant is necessary good sound clinical judgment [8]

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b. *Hyperglycemia* in the *two hour postprandial* specimen if *glycosuria* is *absent* in the fasting state. This will obviate the need for a time-consuming glucose tolerance test except in the case of "borderline or doubtful" hyperglycemic values. The simultaneous appearance of glycosuria with normal blood sugar values in the two hour postprandial specimen suggests non diabetic or benign glycosuria. A glucose tolerance test and identification of the urinary sugar are required for the diagnosis in this instance.

c. An abnormal *glucose tolerance test*. This procedure should be resorted to only because of

1. *borderline hyperglycemic* values in either II*a* or II*b* suggestive of diabetes, *e g* between 120 and 140 gm per cent by the Folin-Wu method.
2. *Glycosuria* in the presence of *normoglycemia* in either II*a* or II*b* suggestive of nondiabetic or benign glycosuria.

The *clinical* diagnosis of diabetes is equally as *important* as its *chemical confirmation*. Glycosuria, hyperglycemia or impaired glucose tolerance cannot make the diagnosis alone; they can only be used to corroborate it. Failure to integrate the chemical data with the clinical manifestations leads to *erroneous diagnosis* and *treatment*.

False stigmatization of normal individuals as "diabetic" subjects them to unnecessary treatment and anxiety, and jeopardizes their insurability. These victims account for almost 15 per cent of all patients *seeking treatment* at Joslin's clinic.[6]

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In the absence of glycosuria and related symptoms, the physician may ignore clinical evidences of diabetes and erroneously dismiss a *bona fide* case of disease as "normal". The diagnosis of diabetes may never be established definitively in some borderline "incipient" or "potential" cases in whom mild abnormalities of carbohydrate metabolism persist without progression for many years.

The physician cannot delegate the responsibility for the diagnosis of diabetes mellitus to a laboratory on the basis of a few drops of blood or urine. "A very important adjuvant is necessary ... good sound clinical judgment."[5]

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Chapter 33

TREATMENT OF DIABETES MELLITUS

By Henry Dolger, M D

Introduction.—Present day treatment of diabetes mellitus in man is reduced to *symptomatic therapy* and is not directed at the cause of the disease. The brilliant advances which medicine has made in the treatment of infectious disease stem from a well grounded heritage of pathology and bacteriology, isolation of the responsible etiologic agents, and then the logical evolution of *specific* chemotherapy. Unfortunately this pattern does not hold true for diabetes since *palliative* treatment, diet and insulin, has been developed before the *fundamental causes* have been discovered. Although the latter remain unknown today, their *intermediary* expression, *insulin insufficiency*, responds to treatment. However, insulin is *incomplete* replacement therapy, except in the rare instance of total extirpation or destruction of the pancreas. Diabetic therapy based on *empiricism* results from the multiplicity of unknown possible etiologic or precipitating factors and the varied clinical manifestations of the disease.

This lack of fundamental knowledge as to the origins of the disease and several special attributes peculiar to diabetes make its treatment more a matter of religious dogma than that of any other medical condition. Sectarianism of unusual extremes for modern medicine characterizes the history of diabetic treatment, not only with respect to the choice of diet and type of insulin but also with regard to its objectives.

In the pre-insulin era the adherents of the "oatmeal," "potato" or "milk" diets and total starvation each proclaimed their respective program with zealous fervor. Fanaticism even extended to the point of locking the patient in a room for several months in order to obtain "cooperation." Many lives were unquestionably saved by the Allen[1] regimen of total calorie restriction but the desperation of patients subjected to its diet of thrice cooked vegetables, olive oil and bran is pitifully illustrated in the case of an emaciated 12 year old boy, almost blind from diabetic retinopathy, who surreptitiously ate his tooth paste and the bird seed of his pet canary.[2] A further indication of the religious quality of treatment at that time was the selection of Sunday as a "metabolic fast-day" in order to "atone for any chance indiscretions."[1]

The inflexible ritual of the daily insulin injection, the veneration of the sugar free urine and the taboos of diet with a sense of guilt on partaking of the forbidden sweet are all part of the religious discipline of diabetes. In the physician is vested the power to reward the patient with an extra slice of bread or to impose a "penance" of further carbohydrate restriction.

Evolution of Current Variations in Diabetic Treatment.—The advent of insulin in 1922 permitted the use of a higher carbohydrate intake. The

diabetic diet today ranges from a low (100 gram) carbohydrate content[4] with equally wide variations in protein and fat. Lawrence[10] fixes the carbohydrate intake at 200 grams or more and permits unlimited protein and fat. A recognized authority exists for whichever standard one might adopt.[4] The increasing use of a normal unrestricted diet for insulin-treated patients[4,4] in recent years has further intensified the acrimonious dispute which rages around this subject. In 1857 Piorry[7] fed 125 grams of candy daily to diabetic patients as compensation for the loss of sugar to the body economy; today Rabinowitch[8] prescribes 20 to 80 grams of *sucrose* whether or not insulin is used.

Before 1922 Joslin's[4] *catechism* "What are you to do with an apple?" was to be answered "Give it away." Today he would accept the reply "Eat it." "Put sugar on and eat it" might be considered the appropriate answer for Rabinowitch,[8] while Tolstoi[4] probably would prefer "Eat it as apple pie."

The longer a person has had diabetes the more he tends to deviate from the prescribed diet until a normal food intake is finally approximated in about 70 per cent of all patients.[11] At the Joslin Camp 61 per cent of the boys admittedly did not follow a diet at home.[12] Obviously any marked divergence from a normal diet cannot be adhered to accurately for more than a limited period of time in most instances. Even Demosthenes in his *Third Olynthiac*, complained of "the diet prescribed by doctors which neither restores the strength of the patient nor allows him to succumb."

The Diet in the Treatment of Diabetes.—It is now generally accepted that the diabetic patient's diet should approximate the "normal" allowances recommended by the National Research Council. Obesity and complications such as hyperthyroidism are typical exceptions which justify either a decrease or an increase in nutritional requirements. Even today according to Carlson[14] "we . . . do not have sufficient knowledge to outline the components of an optimum diet." That a large number of normal individuals do not partake of a nutritionally adequate "normal" diet is well recognized. If a non-obese diabetic patient cannot maintain weight, vigor and health on such a diet, it is not justifiable to resort to rigid restriction of the carbohydrate content in order to avoid the use of insulin.[15] It is impossible to determine a patient's actual food requirements by any mathematical formula. These vary extremely from patient to patient; the final result of maintenance of weight (and growth in children) will indicate the adequacy of the diet.

Since *nonavailable* carbohydrate had been included formerly in the standard commonly accepted food values, the latter had to be revised downward.[15,16] Official corrections of these inaccuracies in *available* carbohydrate content of foods have been promulgated by both the American Dietetic and the American Diabetes Associations. A greater latitude in diet is therefore possible now even for those subject to rigid carbohydrate restriction.

Ice cream and *sponge cake* appear on this officially approved list as acceptable equivalents of 1 slice of *bread* with respect to carbohydrate content. An average scoop or brick of ice cream yields 15 grams of carbohydrate; a Dixie cup or Melorol 12 grams. Furthermore the traditional

—

diabetic dessert of fruit produces a more exaggerated hyperglycemia than that of the slowly available carbohydrate in ice cream.

The following analyses[14,15] of several unorthodox desserts indicate their suitability for diabetic patients by any standard of therapy when the archaic emotional prejudice against "sweets" is put aside.

TABLE 83

	Per cent Sugar		Per cent Sugar
Ice Cream	17.5	Fresh Orange Juice	13.1
Apple Pie	17.3	Unsweetened Grapefruit Juice	10.3
Coconut Cake	16.0	Cola Drinks	10.5
Banana Custard	13.8	Gingerale	9.0
Chocolate Pudding	13.4	Cream Soda	11.0
Tapioca Pudding	11.6	Sarsaparilla	10.0
Rice Pudding	10.9	Orange "pop"	14.0

No significant differences in the *insulin requirements* of either diabetic children[18] or adults[19] are noted when isocaloric substitutions are made with high fat *versus* high carbohydrate diets.

THE INITIAL APPROACH TO THE TREATMENT OF THE DIABETIC PATIENT

Where.—1. *Hospital* treatment should be reserved for diabetic emergencies (ketosis and coma) and complications.

2. *Ambulatory* treatment directed from the office or clinic is applicable in most other instances for the initiation or regulation of the diabetic regimen. It is unrealistic to hospitalize the average patient because the prime goal of treatment should be the achievement of a therapeutic program adequate for the every-day routine of the patient living in his usual environment. The atmosphere of a hospital is artificial, with abnormally close approximation of meal schedules and lack of physical activity. Bouchardat,[20] the greatest clinician in the history of diabetes,[21] pointed out the fallacy of hospitalization one hundred years ago. He noted the unpalatability of hospital food, the cold meat courses, the unnatural physical restriction and the depressing atmosphere. All too often a painstaking regimen which has been obtained after several weeks at a hospital must be altered markedly to meet the usual demands of normal living. The art of the physician is called upon to provide a therapeutic program geared to the patient's *actual*, not theoretical, needs.

When.—1. *Immediate* treatment with insulin should be initiated when marked glycosuria, with or without acetonuria, is found in association with the classical symptoms of diabetes. There is *no* need to delay this until the result of a blood sugar determination is finally obtained. Naturally, immediate treatment is the purpose in hospitalizing the patient with a diabetic emergency.

2. *Delay in treatment* can be afforded in the absence of the above. Casual glycosuria or asymptomatic diabetic manifestations permit temporizing until a definitive diagnosis is established.

What—1 *Dietary restriction of carbohydrate* alone is adequate initial treatment in the case of the obese or asymptomatic patient despite marked glycosuria

2 *Insulin administration* is indicated in the initial treatment of the patients with symptoms, and in the presence of infections etc This is especially true of children and about one-half of adult diabetic patients Concurrent dietary restriction will be required depending upon the nutritional state of the patient being most desirable in the obese individual with classic symptoms

TREATMENT OF MILD DIABETES

Since at least 50 per cent of adult diabetic patients can be treated without insulin some form of mild to moderate carbohydrate restriction is ample compensation for the mild insulin insufficiency This may be accomplished by one of the following

1 *Low total calorie* intake (800 to 1200 calories) for the obese patient

2 *Simple omission* of sugar pastry and soft drinks for the non-obese patient displaying little or no glycosuria This is particularly applicable in the case of elderly individuals

3 *Reduction of carbohydrate* intake to 150 grams with adequate fat and protein in the case of the average vigorous adult with moderate glycosuria or

4 *Unlimited protein* and *fat* intake with reduction of carbohydrate to 100 to 120 grams initially gradually raising it to 150 grams as tolerance improves

Treatment of the Obese Diabetic—The concept that all obese individuals represent a compensated diabetes has been presented Only 5 per cent of these present actual diabetes and of this group a minority regain normalcy by losing weight and reducing the metabolic demand [1] Unfortunately the psychogenic factors in the etiology of obesity are often unrecognized or untreated thereby explaining the therapeutic failures in many instances [22] The use of amphetamine and dexedrine sulfate is not infrequently a valuable adjuvant in the absence of cooperation in dietary restriction Diabetes is not a contraindication to the administration of these anorexigenic drugs [23] contrary to popular belief Doses of d l amphetamine (*Benzedrine*) and d amphetamine (*Dexedrine*) sulfate up to 10 mgs t i d a c have been employed successfully without untoward reactions

The optimum dietary restriction varies just as in nondiabetic obese individuals 1200 to 800 calories being prescribed according to the need of the patient and the ability to adhere to the program A number of obese diabetic patients requiring insulin are able to discontinue it after appreciable weight loss as illustrated by the following case

Illustrative Case

A forty three year old obese woman had been treated for diabetes for five years With 35 units of protamine zinc insulin glycosuria had been constant and a fasting blood sugar level of 242 mg per cent was obtained before the initiation of a weight reduction regime She weighed 292 pounds at that time the ideal weight being 142 pounds

Using an 800 calorie diet aided by 10 mgs of Benzedrine t i d the patient lost 30 pounds in one month At this time insulin was discontinued as glycosuria and hyperglycemia disappeared After a total loss of 77 pounds a normal glucose tolerance curve was obtained

Comment —Even though the patient had not attained her ideal weight all evidences of diabetes disappeared shortly after sharp curtailment of the excessive food intake Subsequent failure to maintain this regimen and weight was associated with the return of diabetic symptoms and the reinstitution of insulin

Treatment by Simple Omission of Concentrated Sugars — The avoidance of concentrated sugars in the form of sucrose pastry and soft drinks is a simple and practicable form of treatment for the patient with asymptomatic, transient or casual glycosuria as well as the patient in whom hyperglycemia without glycosuria has been found accidentally These middle aged and elderly individuals need no more elaborate dietary restriction in the absence of obesity Treatment directed at the elevated blood sugar level by more drastic means disregards the patient s well being the primary aim of good medicine

Most observers [3-5] countenance hyperglycemia if adequate nutrition is maintained and *gross* glycosuria avoided In such instances fasting blood sugar values of 200 mg per cent should be acceptable to the physician without arousing fear of delayed healing accelerated vascular damage or acidosis These patients may continue to display hyperglycemia with little or no glycosuria for many years without appreciable fluctuation Elderly individuals comprise a substantial proportion of this group of patients, in view of the relatively higher renal threshold associated with advancing age What purpose is served by more energetic measures aimed at a theoretical but unrealistic optimum? Since there is no loss to the body economy in the absence of significant glycosuria what is the danger of hyperglycemia *per se*? Actually there is no proof of further loss of carbohydrate tolerance or unusual tendency to infections or ketosis [9, 4] or premature arteriosclerosis [26] In fact many observers [27] consider the use of insulin in such patients as contributing to the rapid development of diabetic retinopathy and other vascular complications

The following case histories illustrate the above

Illustrative Cases

A fifty two year old man had noted thirst and polyuria without loss of weight over a period of three months He admitted to the ingestion of at least 1 dozen bottles of soda pop daily in order to assuage thirst Marked glycosuria and a fasting blood sugar level of 260 mg per cent established the diagnosis Simple abstention from the sweetened drink without further alteration in his usual dietary habits sufficed to abolish the symptoms promptly Within one month a normal fasting blood sugar level and glucose tolerance test were obtained In the intervening six years he has remained aglycosuric and normoglycemic on an otherwise normal diet

A sixty nine year old vigorous and active woman was discovered to have a trace of glycosuria on a routine urinalysis She had no symptoms of diabetes and no degenerative stigmata A fasting blood sugar level of 212 mg per cent was obtained No dietary restrictions whatsoever were prescribed and during the succeeding ten years she has continued a fruitful and happy existence

unaware of occasional mild glycosuria and constant hyperglycemia. At the age of seventy five she suffered an attack of acute appendicitis, traveled 500 miles back to this city and when operated upon was found to have had a perforated gangrenous appendix with peritonitis. A remarkably uneventful recovery took place aided by the administration of penicillin and streptomycin. During the period of intravenous glucose feeding 20 units of regular insulin were administered daily but were promptly discontinued when the patient was fed orally.

Treatment by Limitation of Carbohydrate Intake.—In the average adult of *normal* weight, mild to moderate glycosuria with or without classic symptoms of diabetes warrants a therapeutic trial of carbohydrate restriction alone. For simplicity and convenience a level of 150 grams of carbohydrate is set with fat and protein in whatever amounts the patient is accustomed to. This ordinarily provides from 1500 to 2000 calories and still permits fairly close approximation of a *normal* and optimum *American* diet as illustrated:

Breakfast	1 portion of any fruit 1 slice of bread and butter 1 egg coffee and cream
Lunch	1 sandwich of meat, fish or cheese or 2 slices of bread and 1 average serving of meat, fish or cheese unlimited amounts of any green vegetables 1 portion of any fruit coffee and cream, or tea
Dinner	Same as lunch above—at either meal a starchy vegetable, rice, potato, corn or noodles may be substituted in an average serving for 1 slice of bread
On Retiring	1 glass of milk or 1 portion of fruit 1 slice of bread or 3 crackers and cheese

If glycosuria persists after one to two weeks without symptoms of thirst or polyuria, further reduction in the carbohydrate content is warranted with concomitant increases in protein and fat in order to maintain weight and vigor.

The following *high protein, high fat, low carbohydrate* (100 gram) *diet* is essentially a modification of Rollo's[23] original contribution of 1797.

Breakfast	Tomato juice in unlimited amount 2 eggs and bacon 1 slice of bread and butter coffee and cream
Lunch & Dinner	Unlimited amounts of meat, fish and cheese unlimited amounts of any green vegetables 2 slices of bread and butter coffee and cream
On Retiring	3 crackers and cheese or a portion of fruit

linkages of the hormone results in a 50 per cent decrease in its physiological activity[24] The latter is not dependent on the free amino groups of its constituent amino acids but does require the presence of intact *tyrosine hydroxyl* groups[25]

Although irreversibly inactivated on treatment with alkali, in the acid medium in which it is available commercially, insulin withstands boiling for three hours with a loss of less than half of its physiologic activity[26]

Stability of Insulin —*Regular* or unmodified, soluble insulin and *crystal line zinc insulin* are sufficiently stable at *room temperature* so as *not* to require refrigeration ordinarily Under these conditions, the loss in potency amounts to but 10 per cent over a two year period[26] which is not significant for practical purposes Neither is the activity of this type of insulin altered by freezing An expiration date two years from the time of marketing is indicated on the package of every vial

Protamine zinc insulin and *globin* insulin with zinc are less stable and more sensitive to changes in temperature Therefore the expiration date is set at one year from marketing time *Freezing* alters protamine zinc in sulin to the point of uselessness precipitating the suspension in large gran ular sandy particles Allowing this insulin to remain in the glove compart ment of a car or on a window ledge during the winter months results in just such destruction Both protamine and globin zinc insulin withstand deterior ation at ordinary room temperature for considerable periods however, so that refrigeration is *not* necessary during the period of current use[26] Only the reserve supply need be stored in a *cool* environment

Absorption of Insulin —Injection *via* the subcutaneous or intravenous route remains the only efficient means of unmodified insulin administration today Protamine and globin zinc insulin and mixtures of various types of insulin are limited to the subcutaneous route Attempts at sublingual oral percutaneous and rectal administration have not yielded significant effects Dr Harold A Abramson and I obtained but slight hypoglycemic effects from massive doses of insulin administered either by iontophoresis or aerosol inhalation

On injecting insulin labeled with radioactive iodine Root *et al*[27] noted variations of about 20 per cent in the rate of absorption from the subcu taneous areas in normal and diabetic subjects Absorption was appreciably delayed when the insulin was administered into a fat pad (commonly developed at the site of too frequent injection) or in patients with insulin resistance Insulin absorption was rapid during the first two hours amounting to about 40 per cent in this time and then became progressively slower during the next four to six hours

Variable absorption depending on the site of injection may account for some of the irregular effects of insulin with which most clinicians are familiar One young man complained of severe hypoglycemic reactions appearing every fifth day Questioning his technic elicited the information that the mid abdomen was the site of injection chosen on the days of such reaction, whereas the extremities were used the other four days Absorp- tion from the loose subcutaneous tissue of the abdomen was probably more rapid than that in the other areas and may have been enhanced by the massage-like effect of a tight belt

The absorption of protamine zinc insulin is more than a simple physical phenomenon, since Bang[13] has demonstrated this to be initiated by enzymatic splitting of the insulin complex

Types of Insulin Available —Rapidly acting unmodified soluble insulin is available in 2 forms which are interchangeable and *identical in* physiologic activity 1) amorphous or *regular* insulin and 2) solution of zinc insulin crystals, the latter being recrystallized from the former with the aid of zinc This original clear form of insulin is the basis for the modifications (1) protamine zinc insulin (2) NPH and (3) globin zinc insulin which simply prolong its time of activity

Unmodified (both regular and crystalline zinc) insulin protamine and globin zinc insulin and NPH are available in concentrations of either 40 or 80 units per cc in 10 cc vials (commonly referred to as U40 and U80 respectively) More concentrated solutions of crystalline and protamine zinc insulin in the form of U100 and U500 (the latter as crystalline zinc insulin only) can be supplied upon request by Eli Lilly and Co and E R Squibb and Sons

U80 insulin should be used in preference to the weaker U40 wherever possible for the following reasons

1 The smaller volume of injected insulin is not as likely to cause local skin reactions and either fat atrophy or hypertrophy

2 The average insulin requirement of the severe diabetic is about 70 units an amount *which* can be administered in the standard 1 cc syringe only by the use of U80 insulin

3 Since part of the cost of insulin is in packaging and distribution 800 units as 1 vial of U80 will be less expensive than the same amount in the form of 2 vials of U40 strength Cost is an important item in a lifetime disease such as diabetes and any possible economy for the patient is an obligation of the physician

The use of the U40 concentration is indicated however when the prescribed dose is less than 10 units in which case measurement may be difficult or inaccurate with the more concentrated form This is particularly true of juvenile diabetes where doses of 3 to 5 units are not uncommon An example of the ridiculous extreme which some patients may resort to in administering insulin was observed in the case of a diamond merchant who took 22½ units daily using a jeweler s loupe for exact measurement

Sources of Insulin —Mixtures of pork *and beef* pancreas are the usual sources of regular protamine zinc insulin and globin insulin with zinc *Insulin derived solely from beef pancreas is available commercially* in the form of regular and protamine zinc insulin (Lilly U40 and U80) in vials stamped with the label *Special* in red ink The same types and strengths may be had in an all *pork* insulin upon direct request only from Eli Lilly and Co Indianapolis Ind For some peculiar reason Squibb s crystalline zinc insulin is derived entirely from beef *pancreas* while mixtures of hog and beef insulin are used for its other types

Unmodified Insulin (Regular, Crystalline Zinc) —This soluble clear form of insulin in an acid medium is rapidly absorbed a fairly prompt effect being demonstrable within *one hour* Its *peak* action is reached *two to four* hours after injection and dwindles rapidly thereafter being expended in six to

eight hours The size of the dose determines the duration of action, and both rapid and slow acting insulin display a more prolonged effect with larger doses

Rapidly acting unmodified regular insulin is useful in the following instances

1 *Emergencies* such as diabetic acidosis and coma

2 *Fluctuating* and *labile* states characteristic of surgery infections, trauma and other acute complications

3 The *elderly arteriosclerotic* or *cardiac* patients who cannot tolerate even small doses of protamine or globin zinc insulin without suffering nocturnal *hypoglycemia* In these patients a single dose of 10 to 20 units of regular insulin before breakfast appears adequate in obtaining minimal glycosuria during the rest of the day without resort to a second injection

4 As a *supplement* to protamine zinc insulin administered either separately or as a mixture

5 A few "*brittle*" diabetics whose erratic and labile requirements preclude any fixed insulin time action Unquestionably the *flexibility* of this insulin is superior to that of the larger acting ones in such patients and outweighs the disadvantage of multiple injections

Protamine Zinc Insulin —Many investigators tried to prolong the action of insulin using combinations with tannic acid alum, oil and similar substances In 1935 Hagedorn and his coworkers[39,40] succeeded in obtaining a duration of 12 to 16 hours of insulin activity using a simple protamine derived from fish sperm The addition of zinc (0 2 mg per 100 units) to protamine insulinate[41] improved the stability of the compound and led to further prolongation of its activity (24 to 36 hours) This permitted the substitution of a single daily injection in place of multiple ones for many patients Although 0 67 mg of protamine would completely precipitate 100 units of insulin theoretically twice as much (1 25 mg per 100 units) is used in the commercial preparation in order to insure total conversion to an insoluble form This also has an effect in combining with the tissue proteins at the site of injection thereby delaying absorption and prolonging activity still further In addition an excess amount of free unbound protamine will combine with a definite amount of unmodified regular insulin when the latter is added to protamine zinc insulin thus converting it into the insoluble form of the latter The pH of protamine zinc insulin is maintained between 7 1 and 7 4 by means of a disodium acid phosphate buffer

Time activity —Whereas regular insulin is extremely soluble in tissue fluids, protamine zinc insulin is released very slowly its initial weak effect being first demonstrable *after* four hours Peak action is obtained eight to twenty four hours after injection while some residual activity continues into the second day depending upon the size of the dose Once overlapping effects have been established by the consecutive daily administration of this insulin, the activity appears to level off at a more or less constant rate throughout the day[42] Therefore any evaluation of its effect or a change in the dose should *not* be made on the basis of *less* than several days observations This relative *constancy* of action may result in the following difficulties

1 *Insufficient intensity* of insulin effect during the day when *glycosuria* may be excessive as the maximum load of exogenous carbohydrate is ingested

2 *Excessive* insulin effect during any prolonged fast, especially during *sleep* These effects are noted regardless of the *time* of injection whether it be on arising or on retiring

Diurnal glycosuria and *nocturnal hypoglycemia* appear to be particularly disturbing in severe diabetes where large doses of insulin (over 60 units) are required as well as in brittle cases and patients with irregular living habits In the latter delay in the evening meal oversleeping in the morning or unusual physical activity in the late afternoon or at night may lead to severe hypoglycemia The hypoglycemic episodes of protamine zinc insulin are unique in that (1) they often lack premonitory warning symptoms and (2) the duration is so prolonged that the ingestion of the usual amount of carbohydrate may be inadequate and symptoms may recur several hours later Because of this limiting factor of nocturnal hypoglycemia the insulin dose cannot be increased in the face of marked symptomatic glycosuria during the day This situation can be remedied by the use of insulin mixtures or separate injections of regular and protamine zinc insulin The latter technic usually entails the administration of 25 per cent of the total dose as regular and the remainder as protamine zinc insulin

Protamine zinc insulin is *useful* in the following instances

1 The large *majority* of patients requiring *small* to *moderate* doses of insulin (up to 30 or 40 units daily) Satisfactory results can usually be obtained in this range of insulin requirement with minimal glycosuria and freedom from hypoglycemia A very acceptable night snack just before retiring is ordinarily sufficient protection against hypoglycemia in this group of patients This and caution against *delaying* or *skipping* of meals are the only essential dietary measures

2 As a *supplement* to unmodified regular insulin during pregnancy infections and hyperthyroidism and in the routine postoperative care of the surgical diabetic Here the special value of protamine zinc insulin lies in its ability to abolish ketonuria and excessive protein catabolism even in the presence of glycosuria

3 As the basic *component* of *insulin mixtures* in the treatment of severe diabetes including the juvenile and brittle cases as well as the milder cases prone to nocturnal hypoglycemic episodes from protamine zinc insulin alone

Since protamine zinc insulin is an insoluble suspension thorough *mixing* of the vial must be secured just prior to withdrawal in order to obtain *uniformity* and *predictability* of effect. One patient presented periods of ketosis alternating with cycles of hypoglycemia until it was discovered that she had diligently *avoided* shaking the insulin vial She would carefully draw off the inert supernatant fluid by angulating the vial at first and during this period suffered from mounting ketosis which prompted her physician to increase the dose rapidly By this time however a concentrated residuum of protamine zinc insulin would be reached yielding many times the expected dose with the resultant disappearance of ketosis and the

development of severe hypoglycemia as well Apparently this performance was duplicated with each new vial of insulin Stabilization was easily effected thereafter by proper suspension of the insulin before its withdrawal

Particular attention should be given to the *gentle mixing* of a *fresh* vial because of a tendency of protamine zinc insulin to 'clump or to adhere to the glass container on standing for any length of time This not infrequently follows incorrect storage in the coldest part of the refrigerator In such instances, great difficulty may be encountered in obtaining *complete* resuspension thereby reducing the available potency Careful scrutiny of the vial before use should be automatic on the part of the patient

Irregularity of insulin effect may also occur when too *fine a gauge* of hypodermic needle is used The narrow caliber of no 27 gauge needles may not permit complete withdrawal of the particulate insulin material especially after deposits accumulate within the lumen in the course of use Consequently no 25 or 26 gauge needles should be prescribed for the proper management of diabetes with this insulin

Globin Insulin with Zinc —In 1943 another insulin with "intermediate action' was added to the therapeutic armamentarium of diabetes Based on the same principle of prolongation of action as protamine zinc insulin globin insulin is prepared by the addition of purified globin (derived from beef hemoglobin) to unmodified insulin It is a clear pale amber acid solution at a pH of 3 6 containing 3 8 mg of globin and 0 3 mg of zinc per 100 units Its stability at room temperature is less than that of protamine zinc insulin and very much less than that of unmodified insulin The alkaline tissue fluids at the site of injection *precipitate* globin insulin at a variable rate as a relatively insoluble complex This leads to irregular dumping out ' of insulin from its depot at unpredictable rates accounting from some lack of uniformity in its action

Time-activity —Duration of activity varies with the dose as in all types of insulin *Onset* of activity begins within two hours after injection but is extremely slow for the first three to five hours[43] The *peak* of activity is reached in about eight hours and thereafter diminishes rapidly its effect being exhausted in eighteen to twenty hours after injection In comparison with protamine zinc insulin globin offers less constancy of effect a somewhat more rapid onset an intense peak activity at the eighth hour and a shorter duration This leads to the following difficulties

1 *Late afternoon hypoglycemia* due to *excessive intensity* of action *eight hours* after administration

2 *Nocturnal glycosuria* associated with disturbing polyuria due to *insufficient effect* after eighteen to twenty hours As with protamine zinc insulin these undesirable features appear most commonly in the severe diabetic requiring more than 40 units daily and the brittle case

In addition 4 P M *hypoglycemia* frequently disturbs the patient using even smaller doses of globin insulin This originates from the inability of the average American worker or housewife to make lunch the heaviest meal of the day The proponents of this insulin agree that the noon meal should equal and preferably exceed the food value of dinner if late afternoon hypoglycemia is to be avoided This poses many problems for the patients accustomed to a light lunch and a main meal in the evening

with the family The program required by globin insulin seems more applicable to the Continental style of eating with its long lunch period and 4 o'clock tea'

The peak hypoglycemic effect eight hours after injection is further intensified by the increased physical activity of work characteristic of that time of day Furthermore the diurnal rhythm of the blood sugar level in diabetes[44] normally leads to the lowest values in the late afternoon

We cannot confirm the purported claims that the use of globin insulin will prevent the appearance of *nocturnal* hypoglycemia or local skin 'reactions' The erratic action of large doses (over 60 units) induced most severe hypoglycemic episodes during sleep in a number of patients Transient local swelling and itching at the site of injection of globin insulin appears almost as *frequently* as with protamine zinc insulin A distinct handicap of globin insulin is the complaint of local burning *pain* in about 20 per cent of patients This may last from a brief moment to several hours introducing an unnecessary disturbing element in the insulin treatment of diabetic children or hypersensitive adults

Globin insulin with zinc is suitable for the following patients

1 The *average* diabetic requiring less than 40 units daily This group can be managed successfully with almost any kind of insulin and regimen With an adequate lunch and a 4 o clock snack the hazard of late afternoon hypoglycemia can be minimized

2 The severe diabetic will require a *supplement* to the single daily injection of globin insulin

a In the event of *nocturnal glycosuria* and *acetonuria*, one third of the total dose may be given as a separate injection of protamine zinc *insulin either on retiring or in the morning* *The 2 types of insulin cannot* be mixed Another therapeutic device consists in giving 2 doses of globin insulin 2/3 before breakfast and 1/3 before dinner

b *Inadequate* prompt effect can be overcome by the addition of 20 per cent of the total dose as unmodified regular insulin administered either *separately* or as a *mixture*

The *advantages* of globin insulin are

1 Its availability as clear solution which does not require mixing

2 Its more rapid but less prolonged effects suited to the less severe diabetic in whom glycosuria is maximal by day and minimal or absent at night

3 Its simplicity as an intermediate insulin for the patient incapable of understanding the technic of protamine zinc insulin mixtures

The *disadvantages* of globin insulin consist in

1 A *lack of uniformity* or *predictability* of action particularly in larger doses

2 An activity curve *not synchronous* with American dietary habits and meal schedules

3 *Inadequacy* of overlapping *nocturnal effect* in severe diabetes

4 *Pain* after injection in a number of patients

Mixtures of Regular and Protamine Zinc Insulin —Throughout this discussion it has been apparent that the vast majority of diabetic patients requiring *less* than 40 units of insulin daily offer no great difficulty in treat-

ment, satisfactory results being obtainable with any type of insulin Ninety per cent of the problems of insulin therapy are encountered in 10 per cent of the patients [45] The latter as well as the milder cases were benefited tremendously by the introduction of slow-acting insulin which reduced the number of injections required each day However, marked postprandial glycosuria and nocturnal hypoglycemia could not be avoided by the use of such insulin alone when large doses were needed and supplementary injections of regular insulin were resorted to Inconclusive earlier attempts at mixing both regular and protamine zinc insulin in the syringe before injection finally attained scientific validity on the basis of investigations by Ulrich[46] and Colwell [47] These observers proved that such *extemporaneous* mixtures could yield predictable results Furthermore variations in the 2 components comprising the mixture produce different degrees of rapid and slow insulin action The resultant flexibility of this intermediate insulin preparation makes it uniquely adaptable to the individual requirement of each patient and reduces the need for multiple injections to but a single one

Action of Mixtures —Ulrich[46] indicated the source of previous clinical failures with mixtures as originating from the *excess* of *protamine* in commercially available protamine zinc insulin This extra protein combines with regular insulin up to its capacity forming *additional* protamine zinc insulin Beyond this point the further addition of regular insulin can be expected to remain free or in very loose combination Since for practical purposes protamine zinc insulin will combine an equivalent amount of regular insulin intermediate acting mixtures can be obtained only by the addition of regular in *excess* of the protamine zinc insulin Increasing intensity of rapid insulin action with decreasing intensity of prolonged effect is obtained simply by adding more regular insulin to the mixture

Apart from the ratio of its components the final time-activity of *extemporaneous* mixtures is altered further by its resultant pH [47] The addition of acid regular insulin (pH 3 0) to slightly alkaline protamine zinc insulin (pH 7 2) in a 2 1 ratio yields a pH of 5 6 This being the isoelectric point at which regular insulin precipitates out in an insoluble form its rapid effect may be somewhat delayed in this type of unbuffered mixture

The Insulin Ratio in Mixtures —Mixtures of regular and protamine zinc insulin in ratios of 3 2 (R PZI respectively) were proposed originally by Ulrich [46] Since then ratios of 2 1 and 3 1 have proven more popular [47, 48] No single fixed ratio is applicable to all patients however because of their different insulin needs varying physical activities and diverse eating habits Adjustments in the ratio must be made to fit specific requirements in distribution of insulin activity for each patient In a majority of instances the appropriate ratio can be obtained without difficulty and maintained without alteration A minority of diabetic patients including those with extremely high insulin requirements the brittle cases and a fair number of children defy standardization of the ratio requiring painstaking modification on the basis of trial and error

The Selection of a Proper Mixture —On the basis that the prompt effect of mixtures parallels the proportion of regular insulin while the prolonged

action is determined by the residue of protamine zinc insulin the following R P/I ratios provide the most satisfactory form of insulin therapy

1 2 1 *mixtures* (2 parts regular to 1 part protamine zinc insulin) yield about 25 per cent rapid action and 75 per cent prolonged effect[48] This distribution of time activity makes this mixture physiologically suited for

a *Nearly all* patients requiring *less than* 40 *units* daily[60] A dose of 40 units for example would be tantamount to separate injections of 10 units of regular and 30 units of protamine zinc insulin Since the technic of preparing mixtures is slightly complicated this group of patients may prefer unmixed protamine zinc NPH or globin insulin which afford adequate coverage at present

b About *one half* of the 'severe' cases requiring *more than* 40 *units* as well as the same percentage of juvenile diabetics[60]

Once a basic experience with this mixture has been established in the course of 1 to 2 weeks, *alterations* in the *ratio* may be indicated as follows

1 Increasing the ratio of regular insulin (*e g* 3 1) in the event of polyuria after breakfast and/or nocturnal hypoglycemia

2 Decreasing the ratio of regular insulin (*e g* 3 2) in the event of noon hypoglycemia and/or nocturnal polyuria and ketonuria

In brief mixtures are *adjusted* to avoid both marked glycosuria and hypoglycemia by finding the minimal amount of protamine zinc insulin necessary to attain these objectives in the early morning and the minimal amount of regular insulin needed for these goals during the day

2 3 1 *mixtures* (3 parts regular to 1 part protamine zinc insulin) yield 50 to 60 per cent rapid activity[62] This distribution is particularly suitable in *young diabetic children* whose active day is restricted to about twelve waking hours with the entire food intake confined to this period An early bed time and the long period of sleep (and fasting) make some of these patients unusually susceptible to hypoglycemia in the early hours of the morning (5 to 7 A M) In the case of such episodes substitution of a 3 1 mixture for the usual 2 1 ratio will obviate the prolonged effect of the latter and still provide sufficient overlapping activity to prevent nocturia and ketonuria

A small number of adult diabetic patients require maximum rapid effect in the morning complaining of post breakfast thirst or polyuria with a 2 1 mixture and require a ratio of 3 1 A few adults resembling diabetic children suffer nocturnal hypoglycemia unless a 3 1 mixture is used

3 3 2 *mixtures* (3 parts regular to 2 parts protamine zinc insulin) yield an activity intermediate between that of protamine zinc insulin alone and a 2 1 mixture About *40 per cent of severe diabetics* requiring 70 or more units daily are better suited by this mixture[60] They require a greater prolonged effect during the night because of the tendency to marked nocturnal glycosuria and ketonuria This mixture is also preferable to a 2 1 ratio in the frequently encountered cases subject to a long interval between breakfast and lunch typified by the average commuter farmer and others who arise early In these instances the rapid effect of a 2 1 mixture provokes hypoglycemia before the noon-day meal

4 1 1 *mixtures* (equal parts of both types of insulin) although theoretically resembling protamine zinc insulin in activity actually yield slight

ment, satisfactory results being obtainable with any type of insulin "Ninety per cent of the problems of insulin therapy are encountered in 10 per cent of the patients"[45] The latter as well as the milder cases were benefited tremendously by the introduction of slow acting insulin which reduced the number of injections required each day However, marked postprandial glycosuria and nocturnal hypoglycemia could not be avoided by the use of such insulin alone when large doses were needed and supplementary injections of regular insulin were resorted to Inconclusive earlier attempts at mixing both regular and protamine zinc insulin in the syringe before injection finally attained scientific validity on the basis of investigations by Ulrich[46] and Colwell[47] These observers proved that such *extemporaneous* mixtures could yield predictable results Furthermore variations in the 2 components comprising the mixture produce different degrees of rapid and slow insulin action The resultant flexibility of this intermediate insulin preparation makes it uniquely adaptable to the individual requirement of each patient and reduces the need for multiple injections to but a single one

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The Selection of a Proper Mixture —On the basis that the prompt effect of mixtures parallels the proportion of regular insulin while the prolonged

3 After gentle mixing invert the vial of PZI and insert the needle of the syringe The PZI will flow into the syringe easily, due to pressure of the air injected initially, and the prescribed dose is withdrawn The syringe now contains both types of insulin

4 An air bubble is drawn into the syringe while it is held vertically and then the latter is inverted several times, rolling the bubble back and forth through the mixture, thereby insuring its uniformity The subcutaneous injection is then made in the usual fashion without any need to expel the air bubble

A photographic illustration of these steps is available for the use of patients upon request of Eli Lilly and Co, Indianapolis Ind

It will be noted that accuracy depends upon

1 Provision for air in the replacement of insulin

2 Withdrawal of regular insulin *first*, so as not to becloud its vial by the accidental entry of PZI

3 Complete admixture being accomplished by means of an air bubble

Obviously extemporaneous insulin mixtures are open to the charges of errors in measurement, variability in dose and effect and complexity beyond the intellectual capacity of some patients The physician cannot prescribe a mixture glibly, without weighing its advantages and indications against these practical considerations He must be prepared to offer painstaking instruction and follow up if valid results are to be obtained with this therapeutic measure A visiting nurse was sent to the home of an elderly woman for whom a mixture had been prescribed the day before The nurse never having heard of insulin mixtures and confused by the written instructions proceeded to concoct the mixture in an original manner She had the patient withdraw the proper amount of each insulin into the syringe and eject it into 1 of 2 sterile tablespoons The contents of both spoons were mixed back and forth in the accepted culinary style and finally drawn into the syringe for injection Unfortunately the next day the patient now more confused than ever by the conflicting methods accidentally boiled the insulin vials instead of the tablespoons

An Error in Fixed Insulin Mixtures Some physicians often prepare mixtures *in the vial* in order to avoid inaccuracy and variability and to spare the patient the daily nuisance of mixing it in the syringe The common practice of withdrawing 4 cc of regular insulin from a fresh vial and replacing it with 3 cc of protamine zinc insulin does *not* constitute a 2 1 mixture In order to comply with legal requirements a variable *excess of* insulin of over 10 cc is provided in each vial Therefore withdrawal of a measured amount is *no* guarantee of the quantity remaining It would be preferable to mix measured amounts of each insulin in an *empty* vial

Oversized vials (20 cc) containing 10 cc of regular insulin (U80) were made available for investigation by Eli Lilly and Co with the view towards possible general distribution as a basis for convenient preparation of mixtures Such vials permitted the addition of any desired amount of protamine zinc insulin and offered the advantages of convenience uniformity of admixture superior to that provided by an air bubble and better accuracy in measurement of the dose[60] Unfortunately this material had to be discontinued its availability to the general public being considered

but definite clinical evidences of rapid effect [51 53] Very few patients require this mixture, in every such instance it is used because of an extremely high insulin requirement (over 100 units) which leads to diurnal hypoglycemia with "surplus regular" mixtures and to nocturnal hypoglycemia with protamine zinc insulin alone

Odd Mixtures —Particular circumstances or peculiar individual requirements may necessitate the use of odd mixtures such as 1½ 1, 2½ 1 and rarely 4 1 This happens not infrequently when very large doses of insulin are used leading to significant differences in time activity with relatively small changes in the ratio For example the spread between a 2 1 and 3 1 mixture in a dose of 120 units may be too large for a facile "switch" in treatment from one to the other in certain patients and an intermediate compromise may be indicated as follows

	2 1	*3 1*	*Compromise*
R	80	90	85
PZI	40	30	35
	—	—	—
Total units	120	120	120

Changes in Mixtures —Patients may require different mixtures with changes in living habits physical activity etc Thus one young woman thrived on 90 units of a 3 2 mixture (54 units of regular and 36 units of protamine zinc insulin) over a two year period When her husband finally returned from military service the prolonged nocturnal effect of this mixture led to hypoglycemic episodes after coitus The same dose (90 units) as a 2 1 mixture (60 units of regular and 30 units of protamine zinc insulin) has been satisfactory in meeting her altered requirements since then with freedom from nocturnal hypoglycemia Seasonal variations also play a role in the delicately balanced insulin requirement of the severe diabetic Increased physical activity during a summer vacation may necessitate not only reduction in the total dose but also change in the distribution of insulin activity The use of mixtures in patients with varying requirements is a constant challenge to the ingenuity of the physician A sound principle is to find a dose of insulin which provides adequate control on *most* days and adhere to it until there is good reason to change [54]

Technic for Preparing Mixtures —Careful instruction must be given the patient as to the rationale and the final insulin equivalents resulting from a mixture as well as in *demonstrating* the proper technic of its preparation The latter is outlined as follows

1 Inject a volume of *air* equal to the dose of PZI into the vial containing the latter insulin The vial is held in the upright position during this procedure which serves to prevent difficulties due to "vacuum" in the withdrawal of insulin subsequently The needle is then withdrawn from the vial now containing an extra amount of air

2 A similar injection of air equal in volume to the dose of regular insulin is made into the vial containing that insulin the vial is then inverted and the dose of insulin withdrawn into the syringe

2 Its stability predictability and simplicity make it superior to extemporaneous mixtures

3 It is moderately flexible permitting the recovery of added regular insulin

In general experience with extemporaneous mixtures led to the conclusion that although the use of a single mixture would simplify the treatment of diabetes there is at present no agreement as to the ideal ratio [41] It is unlikely that any one preparation will ever be found to meet the needs of all patients NPH could however replace protamine zinc insulin in the treatment of all but a small fraction of diabetic patients

Particular care in obtaining complete suspension is necessary when NPH is used because of its unusual tendency to precipitate in a tenaciously adherent manner especially in the cold due to its crystalline nature This requires *rigorous* shaking (in contrast to the gentle mixing which suffices in the case of protamine zinc insulin) even though foaming may result Less difficulty is noted in resuspending the particles on subsequent days after the initial more violent agitation

Summary of Treatment with Insulin.—The treatment of diabetes with insulin suffers from the limitations inherent in the fact that the parenteral administration of insulin *cannot* duplicate the normal physiologic mechanism with any degree of close approximation The nearest possible approach involves a cumbersome method wherein the basal insulin requirement is satisfied by a small dose of insulin with sufficiently prolonged action while rapidly acting insulin is administered synchronously with each feeding Were it possible to obtain such an ideal insulin schedule by meticulous and exquisite calculation variable and unpredictable results would still obtain because of the multiplicity of factors other than insulin which determine the course of the blood sugar level throughout each twenty four hour period Consequently the choice of insulin for any patient represents a compromise between his theoretical needs and a realistic appraisal of life s many dynamic influences which change constantly from day to day It is possible to meet the actual requirements *roughly* in a vast majority of patients requiring small to moderate doses of insulin with a single daily injection The needs of the remaining patients may be satisfied to a lesser degree by combinations of the various types of insulin with appropriate distribution of insulin time-activity

EQUIPMENT AND INSTRUCTIONS NECESSARY FOR THE PROPER USE OF INSULIN BY THE PATIENT

Essential Equipment —1 *Insulin* the type selected by the physician in the *appropriate* concentration (U40 labeled in *red* or U80 labeled in *green*) An extra vial or two should be held in reserve in a cool temperature with precaution against freezing Regardless of the type of insulin prescribed every patient should also have a vial of *regular insulin* on hand for *emergency* use in case of ketosis

2 *Syringe* preferably the *standard* insulin syringe approved by the American Diabetes Association and manufactured by Becton Dickinson

unwise in view of the possibility of contamination and the question of legal responsibility for the final mixture.[50]

Modified Insulin—NPH.—Hagedorn[39] and Krarup[40] in their original investigations of various types of protamine zinc insulin had developed one modification "insulin 341" which yielded both rapid and prolonged effects. Unfortunately this advantage was overlooked in the premature acceptance of the long acting protamine zinc insulin now available commercially.

In 1942 *buffered* 3:1[48] and 2:1[47] mixtures were prepared as "fixed" stock modifications of protamine zinc insulin with wider applicability than the original. The 2:1 modification was then introduced as NP42.[52] N for neutral pH, P for protamine, and 42 indicating its content of protamine as 0.42 mg. per 100 units. Except for its buffered pH (7.2) the identification with a 2:1 extemporaneous mixture is indicated below.

200 units R+100 units PZI (containing 1.25 mg. protamine) = 300 units of mixture (total content 1.25 mg. protamine) or $\frac{1.25}{3}$ = 0.42 *mg. protamine per 100 units*

The action of NP42 was more rapid than that of a 2:1 mixture because its uncombined regular insulin was in soluble form at a neutral pH. The modification was then changed to NP50 by increasing its protamine content to 0.50 mg. per 100 units in order to obtain further stability. Further refinement led to the current production of NPH[45] which is extremely stable because of its *crystalline* nature (H in honor of Hagedorn and his coworkers who first obtained the crystals).

Action of NPH.—NPH gives promise of eventual acceptance for general use. It is slightly less active in the first four hours than either a 2:1 mixture or NP50 but its fairly sustained action during each of the succeeding four hour periods (17 to 20 per cent) and its total duration of approximately twenty eight hours make it most suitable in the treatment of severe diabetes. Furthermore NPH itself may be modified for quicker action if desired by the addition of more regular insulin, the effect of the latter being quantitatively recoverable in the final response.

In juvenile diabetes and in a number of adults with high insulin requirements, the use of NPH may result in marked glycosuria at 11 A.M. and hypoglycemia at 4 or 5 P.M. These patients are helped either by the addition of 1 or 2 cc. (80 or 160 units) of regular insulin to the vial or by mixing variable amounts of regular insulin (from 10 to 50 per cent of the total dose according to the need for a rapid effect) in the syringe with NPH insulin as described in the preparation of extemporaneous mixtures. Insufficient effect during the night as manifested by polyuria and acetonuria is characteristic of NPH in those individuals requiring over 100 units daily as well as in "brittle" cases.[50] The latter need extemporaneous mixtures of the 3:2 type.

Advantages of NPH.—1. NPH provides an insulin effect which approximates the needs of the *majority* of *mild* cases and about *half* of the *severe* cases[33] more physiologically than either protamine zinc or globin insulin.

Ferric Chloride Test for Diacetic Acid (Gerhardt) is one of the *simplest* but *least sensitive* methods for the detection of ketonuria. The test is performed by adding several drops of 10 per cent ferric chloride in aqueous solution to 5 or 10 cc. of *freshly voided* urine. An initial precipitate is formed which dissolves on the addition of a few more drops of ferric chloride. A *Burgundy red color* is obtained in a positive test, the intensity of color being roughly proportional to the amount of diacetic acid present.

False positive tests which develop in the presence of salicylates or antipyrine can be ruled out by boiling the solution for two minutes. Thereupon the red color will fade and disappear if diacetic acid is its cause since the latter is volatilized on heating. The red color persists after boiling in the presence of salicylates.

Acetone Tests.—(*a*) *Lange's* method consists in adding a few drops of glacial acetic acid to about 10 cc. of urine followed by a few drops of freshly made concentrated sodium nitroprusside solution. On overlaying the mixture with strong ammonia water (1 to 2 cc.) a *purple ring* appears at the juncture of the 2 liquids becoming maximal in intensity within 3 minutes in proportion to the amount of acetone and diacetic acid present.

b) *Rothera's* modification is identical with the preceding except for the substitution of about 1 gram of ammonium sulfate for acetic acid.

c) *Acetone Test Powder* (made by the manufacturers of Galatest, the Denver Chemical Mfg. Co. Inc.) is simpler than either of the above and more suitable for use by patients. Two or 3 drops of urine added to a small amount of the powder on a white surface will yield a purple color varying in intensity with the amount of acetone present. A tendency to oversensitivity with falsely positive results is a frequent criticism of this method.

d) *Acetest Tablets* (made by the manufacturers of Clinitest, the Ames Co. Inc.) is the *method of choice* for use by patients. It is not sensitive to clinically insignificant amounts (less than 1:1000) and therefore less liable than the preceding powder to yield falsely positive results. The test is performed by placing 1 drop of urine upon a reagent tablet, waiting thirty seconds and observing the development of the usual purple color indicating acetone.

Essential Instructions.—The lengthy introduction of the patient to the above parephenalia should be followed by an even lengthier, detailed discussion of the following specific items:

1. **The Insulin Injection.**—*a. Sterilization of syringe and needle* either by boiling for five minutes or by constant immersion in alcohol in a "Steritube" container. Excess fluid within the syringe must be removed by repeated aspiration and discharge of air through it lest it *dilute* and, in the case of alcohol, also *alter* the physical character of the insulin to be drawn up subsequently.

b. Proper mixing of the *vial* in the case of protamine zinc insulin and NPH or of the *syringe* when mixtures are to be used.

c. Proper technic of injection with particular emphasis on sterile precautions, the initial injection of air to replace the insulin to be withdrawn and a *deep* injection of the needle *perpendicular* to the skin (not at an angle). These procedures are pictured diagrammatically in pamphlets available to

and Co, Rutherford, N J The 1 cc models are available for either U40 (No 1YI-40S with units graduated in *red*) or U80 (No 1YI-80S with units graduated in *green*) concentrations of insulin Selection of a syringe *equivalent* in marking to the strength of insulin will avoid the possibility of error in dosage which occurs not infrequently when syringes with dual markings are used A 2 cc standard (B D) U80 syringe (No 2YPI 80S) is available for patients requiring 80 to 160 units These syringes are all graduated in multiples of 2, therefore it is easier for patients to measure 34 units for example than 35 which must be gauged between the lines An extra syringe should be on hand in case of breakage

3 *Hypodermic needle*, preferably of *rustless* or stainless steel, at least ½ to ⅝ inches in length and of 25 to 26 gauge Finer gauge, such as No 27, is permissible only for use with regular and globin insulin An ordinary beveled point is superior to the Huber point in retaining its sharpness A reserve supply of needles is imperative because their points usually become dull after about two weeks of use In addition the possibility of breaking or bending must be considered

Dependence upon a Busher *automatic injector* (Becton Dickinson and Co) as an aid in overcoming the patient's initial reluctance to self administration of insulin should be avoided if possible Not only does it add an unnecessary "gadget to a voluminous outfit of *essential* items, but it increases the possibility of contamination because of the extra manipulation of the syringe and needle

4 *Alcohol* for sterilization of the vial and the site of injection need *not* be pure grain ethyl alcohol *denatured* and *isopropyl* alcohol are equally satisfactory and much cheaper

5 *A sterile case for syringe and needle* is convenient for daily home use and essential for travel Somewhat elaborate plastic outfits are available from either Becton Dickinson and Co or Eli Lilly and Co but the B D Steritube No 300 or the Vim case are simple Merely a metal tubular carrying case the latter may be sterilized easily by boiling along with the syringe and needle at convenient intervals of one to two weeks Alcohol serves as a sterilizing agent in the interior

6 *Identification card* bearing the name and address of both patient and physician and indicating the possibility of *hypoglycemia* and its treatment *with sugar or candy* Standard cards of this type may be procured without charge from any local affiliate of the American Diabetes Association or from E R Squibb and Sons

7 *Ampules of epinephrine* 1 1000 solution should be in the home of patients who are unusually susceptible to severe hypoglycemic episodes or whose residence is at some distance from immediate medical attention in such an emergency

8 *Tests for urinary glucose* either Benedict s qualitative solution or the much simpler Clinitest and Galatest described previously

9 *Tests for urinary acetone and diacetic acid* are important diagnostic and therapeutic aids in the home care of all moderate, severe juvenile and brittle diabetic patients The majority of mild cases do not require this addition to an already burdensome armamentarium

globin insulin makes a sandwich and milk *imperative* at 4 P M whereas a night feeding although permissible is usually unnecessary

3 **The Hypoglycemic Action of Insulin** —The pattern of activity of the insulin to be prescribed should be explained to the patient so that he understands its period of maximum effect Instruction in the use of insulin is incomplete unless it is accompanied by a discussion of hypoglycemia its causes symptoms and treatment as described below

4 **The Effect of Variable Physical Activity** —The potentiation of the hypoglycemic effect of insulin by increased physical activity must be presented to the patient so that he may regulate the intake of food or the dose of insulin accordingly

Transient unexpected periods of severe exertion can be counteracted only by the prior ingestion of any form of rapidly available carbohydrate (*e g* candy coke fruit or juice An informed patient will be on the alert for any sudden or unusual physical effect during the period of maximal insulin activity and can protect himself in this fashion against the possibility of hypoglycemia

Sustained or *intermittent* physical exertion with some degree of *regularity* may be anticipated in many occupations and requires the outlining of a program of insulin dosage and timing adjusted to the particular demands A sedentary executive may find 80 units of a 2 1 mixture adequate for week days while no more than *one half* the dose 40 units may be tolerated without hypoglycemia on *weekends* when gardening golfing and other forms of exercise are customary The reverse obtains in the case of a manual laborer whose weekday requirement of 40 units of protamine zinc insulin may be entirely inadequate for the usually sedentary weekend when physical activity may be limited to viewing television necessitating *twice* the average daily amount of insulin or 80 units Even more intricate adjustments may be required as in the case of a ballet dancer who automatically evolved a satisfactory solution by taking 40 units of protamine zinc insulin when a single performance was scheduled 10 units when 2 daily performances were given and 80 units on Sundays

Naturally *regularity* of *physical activity* is as desirable as regularity of eating habits if marked fluctuations in insulin requirement are to be avoided Nevertheless the demands of modern civilization make this impossible for most patients A farmer hastening to gather in the crop before a storm could not be expected to cease work because of the possible hazard of hypoglycemia The commuter dashing to make the 5 15 P M train home is usually oblivious to the fact that any modified insulin yields its peak activity at that time

Even the *weather* must be taken into consideration as an influence in variations of physical activity Children in whom diabetes is notoriously labile are most affected by alterations in weather which cause wide fluctuations in exercise After several rainy days of mild indoor play the appearance of a sunny day lends itself to a terrific outburst of energy which unless anticipated by a reduction in the current dose of insulin may provoke hypoglycemia

It is apparent therefore that careful planning and synchronization of an insulin program to the patient s needs cannot provide for *unexpected*

patients without charge upon request of either the American Diabetes Association and its local affiliates or E R Squibb & Sons A series of Kodachrome slides depicting all the above technics can be obtained from the Clay Adams Co Inc 141 East 25 Street New York 10 N Y Using an ordinary pocket size viewer the patient may study each step in technic leisurely without fear of usurping the valuable time of the physician or nurse

d Varying the site of injection, using *different* areas on *each* one of the extremities on successive days

e Uniform time of injection each day With slow-acting insulin (globin PZI, and mixtures) any marked variation in the time of injection from day to day leads to irregularities of the overall effect Several hours delay on one day may result in hypoglycemia during the next day because the relative excess of activity available from the day before adds to that of the current insulin dose in a manner exceeding the normal cumulative effect The time of injection should not vary from day to day by more than an hour or two at the most without altering the dose An anticipated *delay* in *breakfast e g* the partaking of Holy Communion requires a 25 per cent reduction in the dose of slow acting insulin the day *before* An extremely late breakfast or Sunday brunch warrants a similar reduction by 25 per cent of that particular day s insulin dose

f Time of injection in relation to meals Since the action of protamine zinc insulin is relatively constant[42] throughout the twenty four hour period the patient need *not* wait for any definite period of time between the injection and breakfast with this insulin It may be administered at the patient s convenience at approximately the same time each day be it immediately before breakfast or after it or even at night With globin insulin NPH and mixtures of protamine zinc and regular insulin synchronization of the rapid effect with postprandial hyperglycemia requires an interval of at least one-half hour between the time of insulin administration and that of the morning meal The same interval obtains with respect to each meal when regular insulin is used 2 or 3 times daily

2 **The Inflexibility of the Meal Schedule** —Regardless of the type of diet prescribed every diabetic patient using insulin is rigidly confined by the latter to an inflexible feeding schedule In this respect diabetes mellitus may be defined as a loss of the elasticity of normal life—meals cannot be omitted or consolidated at whim without hazard The complete removal of dietary restrictions cannot free the patient using insulin from the necessity of counteracting the inexorable effects of a dose of the hormone fixed *in situ* *Regularity in timing* of *meals* and between meal feedings to *match the action* of whatever insulin is selected must be emphasized as the *primary* role of *any* diet in the treatment of diabetes with insulin The *omission of insulin* is *less* serious than the *omission* of *meals* in most instances

The use of protamine zinc insulin in moderate and large doses *demands* a night snack ' *on retiring* as well as *permitting* the same kind of feeding (*e g* milk and crackers) in the late afternoon This is also true of mixtures of regular and protamine zinc insulin with somewhat more prolonged duration than the 2 1 ratio The use of either a 2 1 mixture NPH or

rubber cap from the vial preliminary to withdrawing insulin, or failure to take the wire stylet out of the needle, or forgetting to invert the vial with the result that the syringe fills with air rather than insulin

Despite frequent gross errors in sterile technic patients *rarely* present local infections secondary to the injection of insulin Yet one overzealous physician insists upon his patients purchasing a dozen syringes needles and sterile containers so that he could autoclave a complete injection outfit for each day the patients return at weekly intervals with 7 used syringes

That such a great number of patients can be entrusted with a complicated procedure and the self administration of a potent drug makes insulin therapy a unique phenomenon in medicine and that satisfactory results can be so generally obtained, despite human error and the daily vicissitudes of man s existence is even more astounding

THE OBJECTIVES OF INSULIN TREATMENT

The treatment of diabetes in the past has been predicated on factors divorced from the patient as a whole e g the minimum food intake compatible with the minimum dosage of insulin, the emphasis on glucose *excretion* rather than the amount retained and utilized the arbitrary prescription of rigidly limited diets without consideration of the patient s needs or habits etc A patient-centered approach to the treatment of diabetes with insulin revolves about the following basic three objectives

1 A *diet adequate* to maintain normal weight and strength ensuring a capacity for work and living equal to that of the rest of society Instead of imposing any of the usual stock diet prescriptions which are then modified because of glycosuria the proper therapeutic goal can be better achieved by adjusting the insulin to that intake of food essential for the maintenance of normal weight and strength Dietary invalidism represents incomplete restitution therapy With the aid of insulin the physician can suit any type of dietary contingency indicated by conditions other than diabetes The dietary treatment of the latter can thereby be made secondary to necessarily fixed regimens such as ulcer diets rice or low salt diets low caloric and low residue diets etc

2 *Sufficient insulin* to assure adequate *utilization* of the diet without provoking hypoglycemic insulin reactions on the one hand or the development of diabetic symptoms such as thirst polyuria and loss of weight along with acetonuria or ketosis on the other For the majority of patients this can be accomplished with minimal glycosuria In about one fifth of the patients however moderate glycosuria is unavoidable and acceptable in maintaining clinical equilibrium between the two extremes

3 *Simplification* of the diabetic regimen as much as possible in order to permit continuation of the usual work and living habits of patients Once stabilized diabetes in the average patient offers little intrusion on normal living given a single daily insulin injection and an approximately normal diet The simpler the regimen the fewer the emotional disturbances in both the patient and his family Naturally, more elaborate detailed management is essential during acute infections trauma surgical

variations in physical activity incidental to *normal* living. The ultimate responsibility for successful management of these day to day contingencies must devolve upon the patient himself. He learns how to adjust the dose of insulin accordingly, under the tutelage of the physician. As the adjustments become automatic many a patient, it is commonly agreed eventually "knows more than the doctor" with regard to the individual management of his own case.

5 **The Effects of Intercurrent Illness, Emotional and other Disturbances on the Insulin Requirement.**—Diabetes is *erroneously* considered as synonymous with a predilection towards infection and poor tissue healing in the minds of most patients and many physicians as well. This fear should be dispelled at the initial visit and the patient reassured that only in cases of *untreated, neglected* diabetes and those complicated by circulatory impairment of the extremities may this concept be applicable.

Emphasis is more properly directed and limited to the role of *infections* and *trauma* in *altering* the *insulin requirement* of the average patient. Since any changes in the insulin regimen depend for the most part on the nature of the underlying infection or trauma the responsibility for such alterations *cannot* be delegated to the patient. The automatic adjustments which the patient is encouraged to make with variable physical activity do not apply to illness or trauma. Evaluation of the latter and their relation to the diabetic state requires the judgment of the physician.

The development of any illness or trauma in a diabetic patient requires prompt communication with the physician and examination if the condition warrants it. Despite differences in opinion as to the value of routine testing for glycosuria by the patient the importance of this procedure *and* the determination of *acetonuria* during infections is undisputed. Such information supplied by the patient often enables the physician to direct treatment in the case of minor illness by telephonic communication alone.

The nonspecific stress of *emotional* disturbances affects diabetic equilibrium adversely, even to the point of inducing ketosis. An explanation of this phenomenon is essential lest patients become confused by the erratic course of diabetes during emotional upheavals in the face of uniform intake of food, physical activity and insulin dosage.

These same *emotional* influences probably contribute to the aggravation and increased lability of diabetes which may appear *pre* and *comenstrually*. Purported reduction in the insulin requirement following estrogen administration for menopausal symptoms is most probably an indirect result of improvement in the emotional status alone. In fact I have *never* seen any effect on insulin requirement from estrogen therapy in the *absence* of excessive emotional irritability during the menopause.

Considering the agitation and confusion on the part of patients when the administration of insulin is first proposed, it is a matter of constant amazement that they eventually grasp the complicated details of technic and even learn to manage the intricacies of insulin adjustment. Repeated checking of the procedure is indicated during the first few weeks in order to guard against errors. Inaccuracy in measurement of the insulin because of the introduction of air bubbles into the syringe is a common initial complaint. Bizarre errors may be expected, such as the removal of the

and the continuation of growth in children. As the latter criterion could not be achieved by the limited diets of former years, pediatricians were forced to liberalize the regimen,[5,96,98] a practice which subsequently spread to the treatment of adult patients. At present the daily carbohydrate consumption of the majority of diabetic patients averages 200 grams,[11] while 250 to 300 grams appears to be gaining popularity.[8,19-23] Increased caloric requirements associated with extra physical activity, growth and pregnancy can only be satisfied in the main by an augmented carbohydrate intake. Fat and protein cannot serve as well in view of the expense and unpalatability (by American standards) involved when excessive amounts of these items are prescribed. As much as 400 grams of carbohydrate are required for strenuous physical labor, providing almost 50 per cent of the 4000 calorie expenditure. In general, proper treatment consists in administering sufficient insulin to insure adequate utilization of the individual caloric needs of each patient. Working capacity is highest in the group taking normal foods irrespective of the type of work and age, and lowest in the strict (limited) diet group.[11]

Since the different schools of thought on the treatment of diabetes, even when at odds with each other, aim for normal nutritional standards, it would seem that a great deal of effort is expended wastefully on the part of physicians, dietitians and patients in calculating, weighing and measuring foods only to result in a diet which is normal except for the omission of sugar, pastry and soft drinks.[23] Actually, ice cream, sweet cookies and chocolate, tapioca and rice puddings provide no more carbohydrate than the traditional serving of fresh fruit. Substitution of these more acceptable desserts for the latter is desirable and cannot be discouraged except on the grounds of prejudice. If these items are also made available for the mid afternoon and late evening snack, so essential for the patient receiving insulin, the average "sweet tooth" should be well satisfied. Extreme excesses in this regard may be observed occasionally when diabetic children, having been on markedly restricted diets, are permitted a normal food intake. The initial orgy of the more liberal program soon yields to a more normal pattern of eating. The appetite of normal and diabetic individuals usually provides an automatic physiologic adjustment to their caloric and nutritional needs, except in cases of obesity.

Reducing the diet to a reasonable normal level is of inestimable value physically, psychologically and socially. It establishes an honest patient-*physician relationship based on mutual confidence and the realities of* living devoid of guilt, cheating or lack of cooperation. Furthermore, resort to expensive "diabetic foods" becomes unnecessary along with the extra chores of "diabetic cookery." Finally, with the physician relieved of the customary but time-consuming dietary catechism, his attentions can be focused more properly on the patient's really significant physical and emotional problems which may or may not be related to the diabetes.

Effect on Insulin Requirement.—Despite the numerous observations indicating improvement of carbohydrate tolerance following its increased intake, the erroneous view still prevails that such action affects the *insulin requirement* adversely. Varying the carbohydrate content of isocaloric diets from 72 to 290 grams did not produce significant changes in the

complications, etc., and in the minority of unstable, brittle cases. The use of scales and the weighing of food are being discarded generally in favor of household measurements or the serving of average sized portions.

Indications for Treatment with Insulin.—The addition of insulin therapy to the plan of treatment is indicated:

1. *immediately* in the presence of
   a) ketosis
   b) classical diabetic symptoms without ketonuria
   c) complications such as infection, hyperthyroidism and preparation for operation, when accompanied by glycosuria
2. *after a trial* of dietary restriction alone fails because of
   a) persistent glycosuria (more than traces)
   b) loss of weight and strength (excluding cases of obesity without glycosuria).

Insulin may be safely withheld in elderly patients and those suffering with heart disease if weight and strength can be maintained by mild dietary restriction even in the face of intermittent glycosuria.

The Choice of Diet.—The diet of diabetic patients can be approached with the same general rules which are applicable to the optimum hygiene of non-diabetic individuals, *i.e.*:

1. obesity requires weight reduction by caloric restriction
2. the aged should be maintained slightly underweight
3. the remaining patients should be treated according to normal nutritional standards.

A Normal Diet for the Diabetic Patient.—The use of a *normal diet* in the treatment of diabetes has been handicapped by popular identification with "free"[5,96] and "unrestricted"[98] diets, terms which bear unsavory connotations of undisciplined license akin to "free love." Objective discussion of the subject would be possible if the terms "free" and "unrestricted" were abandoned. No amount of liberty can free the diabetic patient from:

1. the inflexibility of the meal schedule
2. the need for a basic *minimum* of highly nutritive foods containing adequate protein and fat as well as carbohydrate, in addition to optimum mineral and vitamin content, and
3. the benefit of moderation, regularity and routine in all living habits.

The daily recommendations of the National Research Council for the average sedentary normal woman and man range from 2100 to 2500 calories respectively. This average American diet represents about 200 to 250 grams of carbohydrate and 100 grams each of protein and fat, approximating the values advocated by an increasing number of physicians and clinics as the basis for treating most diabetic patients receiving insulin. Although a *normal* diet is actually being prescribed or adopted spontaneously and eventually by most patients on restricted regimes,[11,1] it is usually cloaked in the cabalistic formula of a diet prescription. A patient's actual food requirements cannot be derived by formula in view of the extreme differences from one individual to another and the variations within the same person from day to day. The adequacy of a diet is determined in the long run by the maintenance of weight and strength in adults

fore cannot reflect the loss of more than 20 to 30 grams of glucose except in the case of a much higher carbohydrate intake. In the latter an average excretion of 50 to 60 grams of glucose usually obtains, representing about 15 per cent of the carbohydrate ingested, a value also considered acceptable by Joslin's[8] criteria. Glycosuria of this order of magnitude is compatible with freedom from acetonuria and azoturia,[8] maintenance of weight and strength, improvement of carbohydrate tolerance, normal wound healing,[9] and antibody production,[100] and normal growth and development in children.[97] Premature vascular damage in the diabetic patient *under insulin treatment* is not related directly to the degree of glycosuria and hyperglycemia.[8, 97]

The Standards of Treatment as Based on the Degree of Glycosuria.—

1. The average case with mild to moderate insulin requirements can easily be maintained with little or no glycosuria according to traditional criteria.
2. The elderly, arteriosclerotic patients and those with heart disease deserve persistent mild or intermittent moderate glycosuria as insurance against hypoglycemia.
3. The cases requiring large amounts of insulin, those with unstable, "brittle" diabetes, and the juvenile patients can best be managed within the realm of practicability by the acceptance of glycosuria according to "clinical control."

The Initiation of Insulin Treatment in the Ambulatory Patient.—Theoretically, determinations of the fasting and preprandial blood sugar levels *throughout* the day may be ideal for the evaluation of treatment with insulin, but this approach should be limited research investigations. Practically the same information can be obtained from the results of urinalysis *before each* meal. In order to obtain reliable preprandial urine specimens the patient should be instructed to empty the bladder about one half hour before collecting the test specimen. After the initiation of insulin treatment and the adjustment of the dose to a point of stability, such frequent urinalysis can be abandoned. The occasional "brittle" diabetic patient may need to continue testing the urine as a gauge for the administration of varying doses of regular insulin. The initial dose of insulin cannot be calculated on the basis of a fasting blood sugar level; it usually is derived empirically, depending on the clinical picture as follows:

1. In the case of the *average* adult patient with pronounced classical symptoms of diabetes and marked glycosuria an initial dose of 20 units of regular, unmodified insulin should be administered during the first visit in addition to a *separate* injection of 20 units of protamine zinc insulin.

a) If symptoms improve and glycosuria is reduced or absent in the prebreakfast urine specimen the next morning, only 20 units of protamine zinc insulin should be administered, preferably by the patient himself. Analysis of the urine specimens before breakfast, lunch and dinner for several days thereafter will determine subsequent alterations in dosage. The *continued absence* of glycosuria in the early morning indicates having reached the limit of effectiveness of the protamine zinc insulin dose. Any further increase may invite a hypoglycemic insulin reaction. Therefore the appearance of marked glycosuria, a recurrence of symptoms during the

64

amount of insulin needed to control glycosuria.[19] Similar observations were obtained in diabetic children.[18] Patients frequently report an amazing experience (to them) in the failure to detect glycosuria following over-indulgence in sweets. In fact, Rabinowitch[8] claims that the daily ingestion of 20 to 80 grams of *sucrose* as part of the diabetic diet results in definite reduction of the insulin requirement. An extreme example of sugar consumption has been observed in the case of a sixty-five year old clinic patient with diabetes of fifteen years duration who insisted on taking 50 to 60 *teaspoons* of sucrose daily in various forms in addition to a normal diet. His insulin requirement, 40 units of protamine zinc insulin daily, has not altered in all these years and he has never suffered from ketosis or pyogenic infections despite glycosuria of about 50 to 60 grams per day. The improvement in tolerance even to the point of remission of diabetes, which may follow a short initial period of insulin therapy, is not jeopardized by the use of a normal diet.

Vitamin supplements have *no* significant influence on the insulin requirements despite many uncritical claims to the contrary advocating the use of such vitamins as B Complex and E or the lipotropic factors choline, methionine and inositol.

The Significance of Glycosuria and Hyperglycemia in the Insulin treated Patient.—Happily the heated controversy over the use of a normal diet for the diabetic is approaching reconciliation in the realization of a common goal of optimum nutrition by normal standards. The fury of that dispute, however, has been transferred to the problem of "control" of glycosuria and hyperglycemia. Unfortunately the two issues have become so confused in presentation that a normal diet is considered synonymous with *unlimited* glycosuria by some observers. The distinction between the two is revealed in John's[3] regimen by which normoglycemia can be obtained in three-quarters of the day when a normal diet is used. The most successful regulation of glycosuria and hyperglycemia achieved in actual practice has been that reported by Jackson and his associates.[99] Their strict standards of "control" necessitated the use of multiple injections, regular insulin being given before breakfast and lunch and globin insulin before dinner (the latter replacing regular insulin formerly given at that time and at 1 A.M. in addition). In the course of time, however, they could obtain continuous "good control" in only a *single* patient over a 22 year period. Although they claim that such a "level of control" is associated with a delay in the development of degenerative changes they admit that premature vascular damage is related to the duration of diabetes.

When the administration of insulin is limited to one injection per day some glycosuria becomes unavoidable in most cases requiring more than 30 to 40 units daily and in all diabetic children as well. Consequently, even Joslin[9] countenances daily glycosuria amounting to 20 grams. This is not far removed from the practice of Tolstoi[6] and others[97, 98] who disregard the glucose excreted and measure instead its utilization by the yardstick of "clinical control." They aim for freedom from the diabetic symptoms of thirst, polyuria, etc., the maintenance of weight and strength and the avoidance of hypoglycemia and ketonuria. In reality this requires the utilization of a minimum of 150 to 200 grams of carbohydrate and there-

fasting and preprandial levels should not be permitted to fall much below 150 mg per cent if asymptomatic as well as symptomatic hypoglycemia is to be avoided The many diverse effects of the latter are described in the following section

COMPLICATIONS DUE TO INSULIN

HYPOGLYCEMIC OR INSULIN REACTIONS

Introduction.—*Insulin reactions* constitute the most common as well as the most *serious* complication resulting from the *treatment* of diabetes Although shock is not an integral part of the syndrome the term insulin shock is commonly but erroneously used as a synonym A question as to the hypoglycemic nature of the reaction is posed because the clinical picture need *not* necessarily be associated with subnormal blood sugar values and *vice versa* Experience with diabetic patients and observations in the treatment of schizophrenia with insulin shock' indicate a lack of correlation between *symptoms and blood sugar level* Furthermore *normal* individuals may tolerate large doses of insulin (*e g* 100 units of protamine zinc insulin) *without* symptoms despite marked hypoglycemia[56] in *contrast to the sensitivity of the average diabetic patient to much smaller* amounts of insulin

Relation to Hypoglycemia.—*Failure* to obtain an *absolute* value for the blood sugar within the traditional *hypoglycemic range* of 50 to 70 mg per cent does *not* rule out the diagnosis of insulin reaction since the *rate of fall* of the blood sugar level also determines the onset of the symptoms A disparity between chemical and clinical findings is especially characteristic of *diurnal insulin reactions* which follow in the wake of a *precipitous decline* from *excessive* post prandial *hyperglycemia* to normal blood sugar levels of 80 to 120 mg per cent The rapidity of the rise in blood sugar level determines its rate of fall to some extent and the appearance of symptoms[56] This is observed not only in diabetes (treated with insulin) but in non-diabetic alimentary hypoglycemia and the post gastrectomy syndrome as well

Diurnal insulin reactions are also influenced by 1) the time of peak activity specific for each insulin 2) the diurnal rhythm of the blood sugar level[44] (*lowest* in the *late afternoon*) and 3) the effect of increased physical exertion *Nocturnal reactions* in contrast result *solely* from the unopposed prolonged *action* of any modified *insulin* during the night s fast and are therefore truly *hypoglycemic* in character

Relation to Cerebral Cortical Function.—The *decisive* factor in the development of *insulin reactions is the glucose* content of the *cerebral cortical cell* the *critical* level of which has been estimated as 10 to 11 mg per cent[57] At this basic level cerebral cortical function is depressed to the point of *unconsciousness* but an increase in the glucose concentration of a few mg per cent is ordinarily sufficient to restore consciousness and other specialized activities[57] This may not occur however despite normoglycemia or even hyperglycemia when the hypoglycemia has been prolonged or severe enough to cause organic damage to the brain

rest of the day, or failure to gain weight indicate the need for additional rapidly acting insulin This can be accomplished by prescribing 30 to 40 units of either a 2 1 mixture or NPH insulin the dose depending upon the severity of the diurnal glycosuria and associated symptoms Between 20 to 40 units will satisfy the requirements of the majority of adult patients

b) Persistence of glycosuria in the pre breakfast urine specimen indicates the need for increasing the dosage of protamine zinc insulin Often 30 to 40 units will abolish glycosuria in this specimen and also reduce it appreciably during the day Such increases are best made in 5 to 10 unit increments and only at 2 to 3 day intervals so as to observe the cumulative action of protamine zinc insulin The same precaution is necessary for the evaluation of changes in any slow acting insulin, including mixtures, NPH and globin A 2 1 mixture or NPH insulin is preferable when an increase beyond 10 units of protamine zinc insulin is required on the basis of the preceding criteria

Stabilization of the insulin dose may be considered as having been reached when symptoms have disappeared normal weight and strength have been restored and glycosuria is absent or only a trace in the morning and minimal during the day (varying from zero to 4 plus) Hypoglycemic insulin reactions indicate the need for appropriate adjustments in dosage or type of insulin

2 In the absence of a complication deserving hospitalization the ambulatory patient with severe symptoms *and* acetonuria in addition to glycosuria should be treated more vigorously Forty units of both regular and protamine zinc insulin should be given separately in the average case and half as much in elderly individuals Twenty units of regular insulin are prescribed at six hour intervals until *acetonuria* disappears while some glycosuria is permitted because of the expected eventual effects from the original dose of protamine zinc insulin The next morning with acetonuria absent and glycosuria still present 40 units of protamine zinc or NPH insulin may be given as a basis for the ultimate insulin program which is evolved in the fashion described in paragraph 1*b*

3 In the patient with asymptomatic glycosuria which does not respond to dietary restriction the initial dose need be only 10 to 20 units of protamine zinc or NPH insulin Subsequent adjustments are made as described above In a number of elderly patients and those with an anginal syndrome 10 to 15 units of regular insulin administered once a day before breakfast would be preferable to protamine zinc insulin which bears the hazard of nocturnal hypoglycemia in such relatively mild cases

4 In patients recovering from an acute complication which required treatment with several injections of regular insulin per day transfer to protamine zinc or NPH insulin or mixtures can be accomplished by administering the latter in an amount equal to three quarters of the total daily dosage of regular insulin Adjustments are then made as described above

The course of the insulin requirement is unpredictable at the beginning of treatment Since rapid recovery of tolerance may ensue it is necessary to watch for insulin reactions during the initial period particularly and to reduce the dosage accordingly *If blood sugar determinations are made* the

hypoglycemia → glycosuria and acetonuria → increasing insulin dosage → hypoglycemia etc This is not an uncommon history in diabetic children and adults especially when overtreated by carbohydrate restriction and the insistent but futile pursuit of aglycosuria

The Provocative Causes of Insulin Reactions — Essentially insulin reactions result from an *absolute* or *relative* excess in insulin activity beyond the patient s need at the moment The triad *too much insulin too little food* and *too much physical activity* encompass the possible precipitating causes Specifically insulin reactions may develop following

1 *Error in dosage* illustrated by the following incidents the unrecognized administration of U 80 insulin in a U 40 syringe the repetition of the insulin injection because of failure to recall having taken it earlier the erroneous administration of a prescribed 2 1 mixture (*e g* 60R + 30 PZI) separately and unmixed One patient having failed to take insulin the day before injected a double dose without realizing the ultimate effect of such error Inaccurate interpretation by the nurse of illegible orders left by the physician accounted for the following accidents 10U insulin being read as 100 insulin and XX units being written almost like XL units Another nurse s error occurred when 30 units of regular insulin (U 80) were given as 30 *minims* or 160 units because only a 2 cc syringe could be found at the moment

2 *Inadequacy of food or interference with its availability* This may follow curtailment omission or delay in meals vomiting pylorospasm or diarrhea A case in point is the omission of breakfast or lunch as a routine preoperative order without consideration of the possible effects from the insulin given not only that day but the day before as well

3 *Unusual physical activity* violent exercise variable physical requirements with changes in occupation season and weather as described previously

4 *Overtreatment* with insulin in the face of decreasing requirement as in

a) the *early* period of insulin treatment when the patient s tolerance may exhibit rapid improvement

b) the *convalescent* stage after illness or operation when the original *catabolic conditions responsible for* an increased insulin requirement have receded *without* simultaneous reduction in dosage and further aggravated by the effect of increasing *mobilization* and ambulation

c) the failure to understand the significance of *post hypoglycemic glycosuria* and acetonuria in the vicious cycle outlined above

5 *Failure to synchronize the timing of insulin activity* with the patients habits and needs

Symptoms — *Premonitory* minor symptoms represent disturbances of the sympathetic nervous system chiefly and include sudden *hunger headache weakness faintness* and *vertigo sweating* paresthesisa of the face tongue and lips visual disturbances tremors and palpitation Unfortunately these symptoms which respond easily and quickly to the prompt ingestion of carbohydrate are either overlooked by the patient engrossed in some external distraction or may fail to appear prior to the onset of more severe neurologic or psychic manifestations A lack of premonitory warning symptoms is often characteristic of prolonged acting insulin not

As the cerebral blood flow remains unchanged during hypoglycemia in the absence of convulsions, a progressive *decrease* in *cerebral oxygen consumption* and *metabolism* which characterizes this state of *reduced glucose utilization* is due solely to deprivation of the chief source of energy.[58] Despite this close correlation of cerebral anoxia with hypoglycemia, the two conditions produce similar but *not* identical histologic lesions in the brain.[59] Depression of cerebral metabolism during hypoglycemia is also indicated by *electroencephalographic* changes in decreasing frequency and final disappearance of the alpha waves and augmentation of the delta index.[60]

Sensitivity of the different areas of the brain to the effects of hypoglycemia depends upon the metabolic rate of each region. The cerebral hemispheres, phylogenetically the newest portion of the brain, have the highest metabolic rate while the medulla, the oldest part, exhibits the lowest rate and continues to function long after depression of the other higher regions.[61] Symptoms develop in progressive fashion according to this functional neurologic pattern as the blood sugar level falls. *Cortical* depression appears first, producing disturbances in speech, orientation, perception and thought. As unconsciousness develops, *subcortical* manifestations become evident with choreiform and clonic movements associated with signs of overactivity of the *sympathetic* nervous system. *Tonic convulsions* follow involvement of the basal ganglia and mesencephalon. Finally the critical stage involving the *medulla* develops with profound coma, extensor spasms, *parasympathetic* overactivity and *loss* of the *corneal reflex*. The latter marks the border of biological reversibility.[61] Recovery following the administration of glucose retraces the above steps in reverse order. In the event of cerebral damage *recovery* may be *delayed* or *incomplete* with residual permanent defects. A *fatal* outcome follows in the case of extensive damage to the brain and medulla.

Effects on Other Organs and Functions.—The central nervous system disturbances of insulin reactions are also exhibited in such related structures as the peripheral nerves and the eye. Repeated hypoglycemia may lead to peripheral *neuropathy* as well as *myelopathy* and to serious injury in *retinal* tissue.[69] In patients with unrecognized vascular damage the very first *retinal* or vitreous *hemorrhages* may appear immediately following severe hypoglycemia. Because of this and the frequent aggravation of preexisting retinopathy by insulin reactions, some ophthalmologists consider insulin a "toxin," an erroneous unphysiologic concept. *Cerebral vascular accidents* may be similar sequelae of hypoglycemia.

Cardiovascular complications of the insulin reaction include the precipitation of various arrhythmias, including auricular flutter and paroxysmal tachycardia, attacks of coronary insufficiency with angina, and carotid sinus syncope. I have seen several instances of fatal myocardial infarction develop in the course of severe hypoglycemic episodes.

In addition to organic disturbances, insulin reactions contribute to difficulties in diabetic management. Hypoglycemia induces hepatic glycogenolysis with resultant secondary *hyperglycemia* and *glycosuria* which may prompt the physician to increase the amount of insulin mistakenly rather than decreasing it. This false move may appear especially justified when *acetonuria*, an index of severe hepatic glycogenolysis, is noted in addition. A sequence of events is thereby set into motion consisting of

intervention of the police is often necessary when insulin reactions result in assault, exhibitionism and pseudo-intoxication

Increasing difficulties of speech thought and action perseveration confabulation negativism psychomotor hyperactivity and pseudo-hysterical states are further serious manifestations Maniacal behavior and impulsive acts of violence follow increasing disorientation and confusion Wanderings delusions hallucinations melancholia, and paranoia, etc are transitions to more severe symptoms Patients in this stage, may be mistakenly admitted to psychiatric institutions

Medico Legal Consequences —In 1939 Adlersberg and I[62] pointed out the medico-legal importance of accidents arising from insulin reactions a subject still deserving of wider recognition and standardization of legal interpretation Should patients be permitted to drive automobiles taxis and buses, pilot airplanes or engage in hazardous occupations? Lawrence[63] cited the example of two R A F pilots whom their squadron leader refused to ground on the basis of insulin treatment because they were his best, most trustworthy" fliers and they went on to participate in the air battles over Britain during the Blitz ' Despite this experience, the operation of a plane should be forbidden patients using insulin regardless of dosage or susceptibility to reactions

There can be no question as to the prohibition of hazardous occupations and the driving of public conveyances for patients requiring insulin The problem of licensing the operators of private cars is open to dispute This is granted in most states upon certification by a physician as to the applicant s freedom from insulin reactions ordinarily In view of the unpredictability of these episodes, however and the vagaries of daily life it would seem that the interests of public safety can be satisfied only by denial of this privilege Obviously this is not feasible *in practice* and most physicians condone it, limiting the restriction to patients who either display frequent reactions or who lack premonitory warning symptoms Individuals subject to marked irregularities in eating and physical activity should also be included in the latter group

A number of suicides have been committed with overdoses of insulin The defendants in three independent murder cases submitted an extenuating plea of insulin reaction in disclaiming conscious responsibility for the crime Two were acquitted and the third served a brief prison sentence indicating the current confusion of the law in this matter The acquittal of a patient who slew her husband is interesting because of the following legal interpretation by the judge The court is entirely satisfied that this woman of highest character of unimpeachable reputation deeply religious the self sacrificing mother of eight living children the grandmother of twenty five who not only raised her own large family to be the finest type of citizens but somehow found time also to train the motherless children of her neighbor to become valuable highly respected citizens of this community should not now be committed to State s Prison for an act which took place in a few minutes at most an act committed at a time when she was in the early stages of an insulin coma and was incapable of deliberation of premeditation and of forming an intent to kill

only during sleep when such oversight is understandable but also during the day. In the latter instances the slow insidious fall in the blood sugar level, during the late afternoon or evening, does not evoke the usual sympathetic nervous system response which apparently is related to a more rapid type of decline. With increasing duration of diabetes patients also seem to lose their awareness of the premonitory symptoms and proceed directly into the more serious manifestations of central nervous system disturbance.

The *central nervous system disturbances* indicative of progressive hypoglycemia begin with vertigo, diplopia, tremor, and ataxia, followed by paresthesias and hypalgesias, aphasia, twitchings, and rigor. Weakness or paralysis of muscle groups in one or more limbs, convulsions, epileptiform seizures, complete unconsciousness and deep coma are the final manifestations. Some present a stereotyped repetition of symptoms with each episode, while others display utterly different manifestations with each reaction.

A wide variety of *mental changes* is displayed during hypoglycemia, from mild anxiety or exhilaration to severe psychotic states. Milder symptoms are initiated by irritability, anxiety, depression, exhilaration or excitability. Partial disorientation and confusion, a tendency to dawdle or loiter, and slowness of thought and action are commonly observed. Lack of will power and inability to make simple decisions may lead to typical *folie de doubte*.

Many illustrations of such mild mental manifestations can be cited. Relatives of diabetic patients should recognize the appearance of irritability, excitability, or hilarity as indicative of an impending reaction and take prompt measures to abolish it. Some patients appear morose, sullen, asocial and misanthropic at the beginning of a hypoglycemic reaction. They may refuse to sit at the table with their families and may leave their company for the isolation of the bedroom. The conduct of diabetic children may vary in the morning and afternoon classes in such a way that ordinarily excellent and attentive pupils may exhibit inattention and misconduct during mild hypoglycemia. Exceedingly polite and considerate patients may display very rude and boorish behavior when hypoglycemic in contrast to their normal demeanor. Because of slowness of thought and action during this state some patients arouse criticism from foremen or employers or they become so embarrassed that they change jobs frequently.

Inability to make the simplest decision is exemplified in some patients while on the threshold of a reaction who are unable to take the food or sugar usually carried for such emergencies, even though these be at hand. Many aphasic syndromes are also reported by patients.

Such mental changes may bewilder acquaintances and relatives who, familiar with the normal personality of the patient, are alienated by these strange and unusual actions which can lead to serious social complications. In one patient such bizarre behavior constituted sufficient grounds for a divorce action.[62] Not uncommonly patients are suspected of alcoholic intoxication because of ataxia, confusion, belligerence, etc. A kindhearted spectator of such behavior in the case of a young man took him to a nearby hotel, paid for a room and put the patient to bed "to sleep it off." The

The differential diagnosis from diabetic coma offers no difficulty on the basis of the therapeutic test the sudden history the general clinical picture of hypoglycemia, and the absence of evidences of dehydration In the case of cerebral vascular accidents and acute alcoholism failure to respond to the administration of glucose affords the only immediate means of differential diagnosis except in the unusual coincidence of either condition with hypoglycemia Epilepsy's *grande mal* is brief enough to distinguish it from insulin reactions

Treatment—Every diabetic patient being treated with insulin regardless of dosage should carry 1 or 2 pieces of lump sugar or candy on his person as well as some indication of the existence of diabetes and instructions as to the treatment of insulin reactions Failure to inform his roommate regarding the significance and treatment of insulin reactions led to the death of 1 patient when the former discovered him in a state of unconsciousness one morning and recalling the regular habits of the patient in taking insulin, proceeded to administer a syringeful (80 units) of insulin A particular hazard exists in the case of patients who live alone

In *mild* or *moderate* insulin reactions the ingestion of a lump or two of cane sugar some candy fruit juice etc is sufficient to abolish the *immediate* effects Because of the possibility of *recurrent* hypoglycemia with prolonged acting insulin this treatment should be *supplemented* by the ingestion of slowly available carbohydrate in the form of milk bread and crackers etc

In *severe* reactions where unconsciousness prevails or the patient is unable to swallow prompt administration of 25 to 50 grams of 50 *per cent glucose* intravenously is indicated Failing this resort may be made to either the subcutaneous injection of 0 5 to 1 cc of 1 1000 solution of *epinephrine* or the introduction into the stomach of *glucose corn syrup* honey or *cane sugar* by means of tube feeding Prolonged duration of severe hypoglycemia warrants the *continued* or *repeated* administration of glucose depending upon the clinical response Recovery does not preclude recurrent hypoglycemia several hours later where insulin with prolonged action has been taken therefore *hourly feeding* of slowly available carbohydrate is necessary until glycosuria is established

As a general rule the appearance of insulin reactions deserves investigation as to the cause Although often unavoidable adjustment of the insulin dose its timing or its unopposed activity may make insulin reactions amenable to correction

FAT ATROPHY AND HYPERTROPHY DUE TO INSULIN

The disappearance of subcutaneous fat at the site of insulin injections was first reported in 1926[66,67] A striking increase in the incidence of this finding was noted three years later by Fischer[68] who observed it in some two thirds of all diabetic children Marble and Smith[69] found it in about one fifth of 500 unselected patients They reported no instances in the adult males contrary to my experience In patients *under* twenty years of age they noted atrophy in almost one half the females and only one-quarter of

She needs no imprisonment to deter her from committing crime in the future. No imprisonment that this court might sentence her to could reasonably be expected to deter others in this community from committing crime."

Sequelae.—Repeated hypoglycemic damage to the brain may result in functional as well as organic disturbances. Episodes unrecognized during sleep can lead to cumulative damage over a period of years. Fischer and I[64] suggested this possibility in 4 adolescent patients whose intellectual capacities (as well as their objective performance of standard intelligence tests) displayed progressive deterioration many years after the childhood period of recurrent hypoglycemia. Postmortem examination of the brain of 1 of these patients revealed a diffuse degenerative cortical and subcortical gliosis and encephalopathy. Others[65] report constant abnormal electroencephalographic findings in 31 per cent of diabetic patients subject to repeated severe insulin reactions.

Gross neurologic disturbances such as hemiparesis, aphasia, etc., may be transitory or permanent, with instances reported wherein the patient has been reduced to idiocy or a vegetative state. *Post-hypoglycemic encephalopathy* results either from severe or unusually prolonged states of hypoglycemia. Elderly and arteriosclerotic patients are unusually susceptible to serious cerebral damage and offer greater likelihood of hypoglycemic accidents when treated with insulin despite constant glycosuria. An extremely wide range of blood sugar level without glycosuria obtains in these patients due to an elevated renal threshold. Complacent satisfaction with sugar-free urines in such instances should be condemned. When a senile patient recovering from cardiac failure refused his lunch on account of nausea, the nurse disregarded the fact that 40 units of protamine zinc insulin had been administered that morning. At dinner time he was found in a profound insulin reaction from which he never recovered.

Diagnosis.—Signs of sympathetic nervous system activity such as *sweating, tremulousness,* tachycardia and dilated pupils with or without coincidental neurologic and mental disturbances are pathognomonic of insulin reactions of mild to moderate severity. *Hypothermia* is often a clue to otherwise unrecognized hypoglycemic episodes in *hospitalized* patients. A glance at the temperature chart may reveal sharp drops at periodic intervals corresponding to the time of peak insulin activity.

With progressively severe hypoglycemia, coma and unconsciousness are associated with gross neurologic disorders and signs of peripheral vasomotor collapse. Sweating, tachycardia and dilatation of the pupils disappear and are followed by a slow pulse and constricted pupils as parasympathetic nervous system overactivity is released. A positive Babinski sign can be elicited during the period of unconsciousness.

The diagnosis should be *suspected* on the history and clinical picture alone since the urine may be positive for sugar and acetone, having been secreted before hypoglycemia had developed. A *diagnostic therapeutic test* is rapidly obtained by the prompt response to the administration of carbohydrate orally or of glucose (25 grams) intravenously. Determination of the blood sugar level is of academic interest and should *not* delay immediate treatment.

taneous desensitization usually develops with disappearance of the lesions.

Cause.—*Local allergic reactions* are caused by sensitization to the *secondary* proteins contained in *all* commercial preparations of insulin as proven by the prompt disappearance of the lesions with the use of purified recrystallized insulin.[6,77] Claims that globin insulin yields a lower incidence of reactions have not been confirmed.[77] Neither the cresol content nor the pH of insulin is responsible for the reaction. Local reactions are aggravated by errors in technic, *e.g.*, injecting insulin too superficially or irritating the skin with alcohol and unnecessary rubbing of the injection site. The rare *generalized allergic* reactions represent sensitization to insulin protein itself and do *not* appear during the initial period of treatment. Typical of other forms of allergy, sensitization is developed *gradually* so that generalized symptoms become manifest only *after* the *first* or *second* weeks of treatment or *immediately* following the *reintroduction* of insulin therapy *after a lapse* of several months or years. The usual nonspecific clinical picture of *generalized urticaria*, dyspnea, stridor, arthralgias, etc., characterize this type of reaction to insulin. Naturally the complication interferes with the planned treatment, and in rare instances forms the basis for resistance to insulin.[78]

Treatment.—*Local cutaneous reactions* are rarely disturbing enough to warrant treatment, especially in view of their spontaneous disappearance within a few weeks. In the case of *severe* local reactions *partial* relief may be obtained by the administration of antihistaminics orally, and *complete* relief may follow the *mixture in the syringe of the latter drugs* (*e.g.*, *0.5 to* 1.0 cc. of Benadryl 1:1000 solution) with the insulin prior to injection.[79] In the rare case of known allergy to either beef or pork protein, insulin derived from one or the other source may be obtained from Eli Lilly and Co. Crystalline zinc insulin yields somewhat less frequent reactions, but this advantage is outweighed by the nuisance of multiple injections needed with its use. Recrystallized insulin[76] is not available at present.

Generalized allergic reactions to insulin respond unsatisfactorily to antihistaminic therapy administered either parenterally or orally.[77] In an *acute* insulin emergency only 2 procedures are available: 1. *rapid desensitization* to insulin, and 2. the use of *denatured* insulin.

Rapid desensitization to insulin, originally proposed by Corcoran,[80] can be accomplished successfully within twenty-four hours according to the program which I have used. *Three dilutions* of crystalline zinc insulin are made: 1:1000, 1:100, and 1:10. Beginning with the weakest dilution, 0.1 cc. is administered initially, followed by an increase of 0.1 *cc. every half hour* thereafter until 1 cc. of the dilution is being given. At this point the same progressive dosage scale beginning with 0.1 cc. is initiated with the next dilution (1:100). In like manner the final (1:10) dilution is approached, progressing through to the final dose of 1 cc. *Undiluted crystalline* zinc insulin is administered *in the same fashion*, beginning with 0.1 cc. (4 units) and increasing the dose by 0.1 cc. *every hour* until the physiologic effect or optimum dose of insulin is attained. When fully desensitized the patient can tolerate any slow-acting insulin without allergic reactions.

Denatured insulin offers the simplest, most rapid means of obtaining urgently needed insulin effects in the presence of severe constitutional

the males, while about one-quarter of *adult* female patients presented the complication

Cause —The lesion which represents the simple local disappearance of fat, is apparently not related to any of the physical factors involved in the administration of insulin other than the possibility of repeated trauma The duration of insulin treatment the type of insulin used and the technic of injection play no role in the development of the atrophy No difference in incidence is noted between patients who sterilize the syringe and needle in boiling water and those relying upon alcohol sterilization nor is the cresol content or pH of insulin a possible cause In fact all attempts at reproducing the lesion in alloxan-diabetic rats have failed [70] Along with other observers [71] I have seen it develop in nondiabetic patients receiving insulin

This disfiguring complication of insulin administration is particularly annoying because of its predilection for adult female patients and children of both sexes It usually appears several weeks after insulin treatment is begun and occasionally several years later Sometimes it is limited to one extremity the others being spared

Treatment in the past has been aimed at varying the sites of injection with emphasis on avoiding the atrophic areas Spontaneous recovery despite the continued injection of insulin in the involved area has been noted [72] Recently Collins *et al* [73] reported dramatic and complete recovery in 7 patients within one month after directing that the injection be repeated daily into the deepest portion of skin depression in the atrophic area Minimizing the volume of injected material by prescribing a more concentrated insulin (U80 or U100) may be of value

Tumefactions or *fatty hypertrophy* at the site of insulin injection are relatively uncommon This nonspecific lesion is similar to lipomatosis histologically, and contains the same constituents as in the non-diabetic fat [4] Attempts to reproduce insulin lipomata experimentally in mice have been unsuccessful [75] Occasionally both fat atrophy and hypertrophy develop in the same individual A fourteen year old girl with diabetes of six years duration sought to obtain some cosmetic benefit from a disfiguring fat atrophy of the arms She transferred the site of insulin injection to the buttocks calculating hopefully upon a similar melting away of the local fat To her disappointment however fat hypertrophy ensued

Avoidance of the involved area for an indefinite time results in fairly rapid resorption of the tumefaction

ALLERGIC REACTIONS TO INSULIN

True allergy to the insulin protein with generalized manifestations fortunately is very rare The term is most commonly applied to *localized cutaneous reactions* at the site of insulin injection and occurs in about 10 to 20 per cent of patients using insulin during the early weeks of initial treatment The usual history consists of local itching pain and variable redness and swelling noted from the very first injection Such reactions appear within several minutes to a few hours and subside spontaneously within a day After two or three weeks of continued administration spon

without hypoglycemia.[82] Such normal variations therefore should also be expected among diabetic patients. Furthermore no standard ratio of insulin need to food intake can ever be established except on an individual patient basis, and even there marked *fluctuations obtain as described previously*.

Just as the causes of diabetes remain unknown, so do the origins of "insulin resistance" in the *majority* of instances. Certain obvious factors *occasionally* induce unresponsiveness to insulin, including allergy to insulin, acute infection, diabetic acidosis, liver disease and hyperfunction of the thyroid and anterior pituitary glands and the adrenal cortex. All these disorders, however, may also occur in diabetes *without* producing this phenomenon. Consequently, most reports on the subject reveal only fruitless results from elaborate investigations for hormonal abnormalities, neutralizing antibodies to insulin, hepatic disfunction, etc. Similarly, "insulin sensitivity" usually defies elucidation except in the rare case of total pancreatectomy and the even rarer association of diabetes with Addison's disease, myxedema and anterior pituitary hypofunction. The average "brittle" case presents marked lability between hypoglycemia and ketosis, often with a dosage limited to but 20 to 40 units a day. Such patients tax the ingenuity of the physician in obtaining a fixed insulin regimen and may require a flexible program of several daily injections of regular insulin.

The treatment of "insulin resistance" consists solely in the administration without timidity of as much insulin as is needed to insure adequate utilization of the diet. Nonspecific therapy directed at the remote possibility of pituitary and thyroid overactivity has been attempted by means of intense roentgen irradiation of either gland or the induction of myxedema by ablation or radioactive iodine with equivocal results in both. "Insulin resistance" is a transitory phenomenon usually, most cases returning to the previous insulin requirement after several months. In rare instances complete remission of diabetes follows a period of "insulin resistance." A twenty-seven year old otherwise normal male who needed 200 units a day during the first 2 weeks at the time of onset of diabetes six years ago and 175 units during the initial four months has been on a normal diet *without insulin for the past five years. In this interval periodic glucose tolerance* tests proved normal until recently when the first evidences of impairment revealed an impending relapse. The infrequent but definite remissions of diabetes which have been reported are as inexplicable as "insulin resistance" *or the variations in insulin requirement of the average "severe" diabetic.*

PREGNANCY AND DIABETES

Before the discovery of insulin diabetes was characterized by an extremely low fertility, a high maternal morbidity and mortality and an even higher fetal and neonatal mortality. Thanks to insulin diabetic women are now equal to normal women in fertility and maternal mortality during pregnancy. Fetal survival however remains below normal although definitely superior to that of the pre-insulin era. At present the overall fetal and neonatal mortality is about 5 times the normal rate.

allergic reactions to insulin. Since the molecular weight of insulin is about that of egg albumin, Dr. Harold A. Abramson first suggested that the former might lend itself to denaturing by heat. We established this clinically in 5 patients in whom the usual severe allergic manifestations failed to appear with the administration of *boiled* commercial insulin. Since insulin withstands boiling for three hours with the loss of less than half its physiologic activity,[38] vials of crystalline zinc insulin (U80) were denatured by immersion in *boiling* water for *thirty minutes*. The following case history illustrates the effect obtained in the other 4 patients as well.

Illustrative Case

A forty-nine-year-old physician with a history of mild diabetes of sixteen years' duration had taken insulin intermittently in the past six years for brief periods. Ten days after the very first administration he developed generalized urticaria, dyspnea and malaise requiring epinephrine for relief of symptoms. Insulin was discontinued and at various times attempts to reinstate it evoked the same generalized allergic pattern regardless of the type of insulin used or the coincidental administration of antihistaminic therapy in large doses.

He presented the classical symptoms of diabetes: thirst, polyuria, asthenia and loss of weight in May 1949, at which time glycosuria (5 per cent), acetonuria (4+) and hyperglycemia (the blood sugar level being 425 mg. per cent) were present. In view of the allergic history, 0.1 cc. or 4 units of crystalline zinc insulin (Lilly) were administered subcutaneously. Within five minutes the patient developed generalized urticaria and laryngeal stridor necessitating repeated injections of 0.5 cc. of 1:1000 solution of epinephrine.

A vial of crystalline zinc insulin (U80) was boiled for thirty minutes as described above and 10 units were injected subcutaneously four hours after the initial allergic reaction had subsided. No allergic manifestations having appeared, this was repeated in an hour and every two hours thereafter. A total of 60 units had been given by the next morning, when glycosuria and acetonuria as well as the diabetic symptoms had disappeared. At that time a blood sugar level of 70 mg. per cent was obtained. Free from all allergic and diabetic symptoms, the patient proceeded on a regimen of 20 units of the denatured insulin twice daily. After one month this was changed to a single daily injection of 40 units of globin insulin because he now planned to return to his native country where the eating habits appeared more suited to the activity of this type of insulin (main meal at lunch, 4 o'clock tea, light dinner). The transfer to globin insulin was effected uneventfully. He has continued his professional activities in the past 2 years without any disturbance from the daily administration of insulin.

Comment.—Once desensitization has been accomplished, almost any commercial form of insulin may be used without difficulty. In 4 other patients protamine zinc or NPH insulin was finally adopted for routine use after desensitization.

INSULIN RESISTANCE AND SENSITIVITY

These states should be considered simply as *diabetes mellitus* in which responsiveness to insulin may be either unusually deficient or exaggerated; they do *not* represent independent conditions. Differences in insulin *tolerance* of several hundredfold are observed among certain strains of mice,[81] while nondiabetic human beings may tolerate as much as 1000 *units*

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excretion in the urine [90] White[53] in applying these observations to diabetic pregnancy proposed a program of intensive hormonal therapy directed toward correcting the imbalance hoping thereby to reduce the incidence of toxemia and fetal wastage She begins treatment as early as the sixth week and continues until the day before delivery prescribing the *daily intramuscular* injection of stilbestrol and proluton in increasing dosage as term approaches Initially from 5 to 25 mg of both hormones are administered depending upon the duration of diabetes and the degree of associated vascular damage, and after the thirty-second week of pregnancy 50 to 125 mg of each are given

The original investigators[90] of the problem of hormonal imbalance in toxemia have since found that an abnormal rise in serum chorionic gonadotropin does *not* always precede accidents of late pregnancy in diabetic women which involve fetal death [91] This has been confirmed recently by Lorance[92] who also found no correlation between this finding and fetal size Furthermore the latter noted that estrogen therapy appeared to influence C G excretion less effectively as pregnancy progressed and that patients often became completely refractory to stilbestrol The fall in serum estrogen and progestin is assumed to be an indication of deficient hormonal production due to premature ripening of the placenta

Unfortunately the value of hormonal therapy in White's[53] series cannot be evaluated since in addition delivery by Caesarian section prematurely in the thirty seventy week was also performed routinely A fetal mortality (limited to stillbirths and neonatal deaths) of 18 per cent[53] resulted from the combined procedures as compared to equivalent rates of 21 4 18 and 12 per cent obtained by others[84 86 87] *without* the use of hormone therapy In fact where substitutional hormone therapy alone was employed *without* premature delivery a fetal mortality rate of 39 per cent obtained [88]

In my own experience with an admittedly small series of 30 consecutive private cases delivered within the past two years the fetal and neonatal mortality rate has been 10 per cent (1 stillbirth and 2 neonatal deaths) This was obtained *without* the administration of any hormone therapy relying solely upon premature Caesarian section in the *thirty-sixth week* in every instance to forestall the possibilities of toxemia and fetal wastage Although a number of different obstetricians performed the sections White's[53] program for the care of the premature infant was adopted uniformly and probably contributed equally to the satisfactory results Of particular interest was the successful delivery of a viable infant by this method in the case of a twenty six year old woman with a twenty two year history of diabetes who presented evidences of vascular damage in the form of retinal hemorrhages and calcified pelvic blood vessels In addition to the existence of these factors ordinarily detrimental to fetal survival she had lost the child of her first pregnancy four years before during the neonatal period At that time she had been permitted to go to term and was delivered spontaneously of a $10\frac{1}{2}$ pound infant following a protracted labor

The influence of hormonal imbalance and its substitution therapy on fetal survival is equivocal and deserves further investigation where is the

The Nature of the Difficulties in Diabetic Pregnancy.—The problems which are unique to pregnancy in diabetes emanate from the following specific disturbances:

1. *Alterations in maternal diabetes* due to
   a) varying insulin requirements,
   b) irregularities of food intake due to morning nausea in the first trimester,
   c) lowered renal threshold with glycosuria more frequent and even less significant than usual.
2. *Increased tendency to antepartum maternal abnormalities*
   a) water retention and edema,
   b) hydramnios,
   c) toxemia.
3. *Increased tendency to fetal abnormalities*
   a) spontaneous abortion and miscarriage,
   b) fetal death *in utero* and stillbirth,
   c) congenital defects,
   d) premature maturation, gigantism.
4. *Increased tendency to partum and post partum abnormalities*
   a) difficult labor because of
      1. oversized infant,
      2. abnormal presentation due to inability of a large head to engage in the pelvis.
   b) decreased neonatal survival due to
      1. unusually prolonged labor,
      2. unusually traumatic labor,
      3. congenital defects, cardiac hypertrophy, etc.,
      4. generalized edema, asthenia and respiratory difficulties due to premature delivery.

Since the duration of diabetes determines the degree of vascular damage,[26] these 2 factors are unavoidable causes of the high fetal mortality.[83] Despite all measures White[83] could obtain only 50 per cent fetal survival in cases where calcification of the pelvic blood vessels indicated advanced arteriosclerosis. Hypertension or albuminuria was noted in 71 per cent of the mothers with stillbirths, long duration of diabetes accounted for 53 per cent of the fetal fatalities, and early onset of the disease led to a fetal mortality of 66 per cent.[83] Congenital defects are also unapproachable therapeutically at present.

It is evident that some of the other problems can be avoided by:

1. *Management of the maternal diabetes*,
2. *Premature delivery* either by induced labor or Caesarian section four weeks before term, and
3. *Particular care of the newborn* not only because of prematurity but also because of a defective viability during the first days of life.

The Influence of Hormonal Imbalance and its Treatment on Fetal Survival.—An alteration in estrogen and progesterone metabolism obtains in toxemia of late (nondiabetic) pregnancy, characterized by an increased serum level and urinary excretion of chorionic gonadotropin, a reduced serum level and urinary excretion of estrogen, and a decreased pregnanediol

Acidosis may arise in the first trimester due to inability to partake of adequate carbohydrate on the basis of morning nausea and in the middle and last trimesters due to inadequate carbohydrate utilization because of the severe urinary loss of glucose secondary to the low renal threshold

Prenatal Complications —Except for spontaneous abortions and miscarriages which in the opinion of different observers[93,94] may or may not be excessive in diabetes the characteristic difficulties of toxemia and fetal death arise *late* in pregnancy Water retention and generalized edema usually respond to salt restriction the *administration of ammonium chloride* (6 12 grams daily) and modified bed rest Hydramnios is reportedly rare[94] or rather frequent[93] depending on the observer

Since about 70 per cent of stillbirths occur *after* the thirty fifth week and since toxemia is an equally late manifestation *routine premature delivery* serves to anticipate and forestall these complications

Premature Delivery —In addition to these prophylactic considerations premature delivery also obviates the *difficulties of prolonged traumatic* labor due to the excessive size of the fetus breech presentation and shoulder dystocia Estimation of fetal size is an unreliable index of the time for delivery

Elective Caesarian section in the *thirty sixth* week is preferable to the premature induction of labor The former may be performed one of two weeks earlier in the face of progressive toxemia with its threat to fetal survival Spinal anesthesia is particularly suitable in that it permits early postpartum feeding so that only about 2000 cc of 10 per cent glucose in distilled water is needed immediately pre- and post-operatively The dosage of slow acting insulin is reduced 50 per cent the day before operation and omitted the day of operation being replaced by the more flexible administration of regular insulin according to the needs of the moment as in the routine care of any postoperative diabetic patient

Neonatal Care —Although abnormally oversized at the time of premature delivery (*average weight 4000 grams—exceeding that normally* expected for the period of gestation) the infants of diabetic mothers often present poor activity feeble respirations dyspnea and cyanosis and brawny generalized edema Instability of the blood sugar level rather than hypoglycemia characterizes their immediate neonatal course

In addition to an increased incidence of congenital anomalies 2 striking visceral changes first described by Miller[65] appear in some of the infants These include *splanchnomegaly* particularly enlargement of the heart and *extramedullary erythropoiesis* manifested by *normoblastemia* both of which subside spontaneously within two months

There is reason to believe that the adrenal cortical response in all premature infants is inadequate This may account in part for the defective viability of these infants of diabetic mothers delivered before term

Neonatal care should be directed at the prematurity and generally reduced viability peculiar to these infants indicated by the following program modified after White[83]

1 Postural drainage
2 Aspiration of (*a*) the upper air passages *with suction* using a No 10 catheter and (*b*) the stomach

efficacy of premature delivery, either by the induction of labor or section has been fairly well established as insuring a lowered incidence of maternal toxemia and fetal mortality. It is apparent also from White's data that hormone therapy does *not* influence the excessive size of the fetus or the development of congenital defects.

Influence of the Management of Maternal Diabetes on Fetal Survival.—1. The one significant factor in the management of maternal diabetes upon which adherents of opposing schools of diabetic control appear to be in agreement concerns the *deleterious* effect of *ketosis* on fetal survival.[83, 84] Episodes of ketosis are associated with a higher incidence of fetal death *in utero*, stillbirths and premature labor.

2. *Hypoglycemia*, on the other hand, does *not* seem to effect the viability of the fetus. Apparently insulin administered to the mother does *not* pass through the placental barrier.[83]

3. Fetal mortality is *unrelated* to the degree of *severity* of maternal diabetes or the *need for insulin*,[84] an observation supported by the same abnormally high incidence in the *prediabetic* phase of maternal existence cited previously.[90]

4. Neither strict diabetic control by orthodox chemical standards nor less rigid "clinical control" by symptomatic criteria appear to influence fetal mortality significantly, the respective rates for both viewpoints being 18 *versus* 21.4 per cent.[83, 84] Glycosuria of as much as 100 to 150 grams per day was obtained in some patients despite almost normal fasting blood sugar levels.[83]

The Management of Maternal Diabetes.—An old concept that the fetal pancreas contributes insulin to the mother has not been substantiated clinically or experimentally.[93] Insulin requirements fluctuate widely during pregnancy without relation to the trimester or any other factor. As many patients present a markedly increased need for insulin as display the reverse while a large minority maintain stability throughout gestation. In addition to alterations in total dosage, the activity of insulin may require *redistribution* during pregnancy. Constant morning nausea may necessitate the use of mixtures with less rapid effect or even postponing the time of injection until noon. In general, patients continue using their previous type of insulin with satisfactory results. Caution is necessary, however, in evaluating insulin requirement on the basis of glycosuria alone since the latter reflects a low renal threshold rather than inadequate utilization of the diet on the basis of insufficient insulin. Otherwise hypoglycemia and secondary ketosis is easily induced. A prompt return to the usual insulin dosage characterizes the postpartum period.

No special food restriction is necessary except in the case of obesity. Instruction should be given as to the optimum *normal dietary requirements* of pregnancy (according to the National Research Council) with particular emphasis on an adequate protein intake. A minimum of 250 grams of carbohydrate, which is about the average daily intake of the normal individual, is necessary. The average normal limit for weight gain, 400 grams a week, should be the guide as to the need for caloric restriction, any tendency to obesity being strongly discouraged.

retardation of growth and sexual development These abnormalities disappeared when it became apparent that the utilization of nutritionally adequate diets was possible with insulin therapy The juvenile diabetic patient is assured normal growth and development today

8 Treatment with *insulin* is required from the very onset of the disease Occasionally a transient remission follows the initial period of insulin therapy permitting the discontinuance of the latter for several months only to be reinstituted permanently thereafter

9 The daily *insulin requirement* of diabetic children *rises progressively* with age increasing growth and duration of the disease finally becoming stabilized when adulthood is reached At this time most juvenile diabetic patients require an average of 60 to 70 units of insulin daily and often more regardless of the type of diet employed or the degree of diabetic control obtained[98] The greatest increments in the insulin dose appear in puberty and adolescence and following bouts of severe acidosis and coma

10 *Extreme lability* in juvenile diabetes makes perfect control almost impossible outside of institutional care according to Joslin and his associates[9] Wide fluctuations between severe hypoglycemia and marked hyperglycemia *inherent in the nature of juvenile diabetes* are further exaggerated by the living habits of children which differ so from those of adults *because of (a) extreme variations in physical activity, (b) concentration* of meals within a relatively short span of ten hours and (c) a more prolonged night fast of ten to twelve hours

11 Marked *sensitivity* or *responsiveness to insulin* typifies juvenile diabetes and leads to more frequent precipitous *hypoglycemic insulin reactions* with minute alterations in the dose of insulin or following any of the variable factors described in the preceding paragraph Such reactions are often severe developing with unusual rapidity in children whose sense of warning may be completely distracted by the intensity of play Nausea and vomiting are frequent initial symptoms of hypoglycemia in diabetic children unlike adults in whom such symptoms usually indicate ketosis only

12 *Emotional disturbances* and psychologic problems related to diabetes tax the capacity of children and adolescents for adjustment to life situations Serious emotional reactions and behavior problems may develop as a result of a multiplicity of factors including (a) the regimentation of diet and living habits (b) the tyranny of the daily insulin injections (c) widely differing reactions of apprehensive parents jealous siblings and uninformed but well meaning teachers and playmates towards the diabetic patient (d) anxiety concerning the dangers of hypoglycemia diabetic coma and the late complications of the disease and (e) fear of limitations on future employment marriage and childbearing At first compliant with the regimen prescribed by physician and parents many juvenile diabetic patients eventually rebel against the program particularly during adolescence[64] Obviously the effects of such emotional tensions upon the stability of the diabetes cannot be salutary

13 The *fate* of the juvenile diabetic patient is still a *matter for grave* concern The prognosis of diabetes in childhood taking a long view is in spite of the progress of dietary and insulin *treatment* more adverse than

3 Placing the infant in an oxygen incubator for four to five days

4 Dehydration by the omission of oral and parenteral fluids for twenty four to forty-eight hours in the case of generalized edema [53] in the absence of the latter initial feeding with glucose or milk formula is otherwise delayed twelve to twenty four hours The former practice of parenteral glucose administration has been abandoned since the blood sugar levels of these infants do not differ from normal in the course of the neonatal period

DIABETES IN CHILDHOOD

Characteristics —Certain features characterize juvenile diabetes and distinguish it from the disease as seen in adults

1 An *incidence* equal in both sexes without special predilection for females

2 A history of pre-existing obesity is notable by its rarity, although the children are often taller than normal at the time of onset of diabetes In contrast to the large number of obese adult patients the majority of juvenile diabetic patients are *underweight* when the condition is first discovered

3 An acute *precipitating* factor is often present because of the frequency of acute infectious diseases in childhood

4 A fairly *abrupt onset* with classical symptoms is usually observed with the diagnosis being relatively simple and immediate Infrequent exceptions to this rule require further laboratory investigation in order to distinguish the condition from non-diabetic glycosuria The presenting symptoms are ordinarily of such *severity* that diabetic children are often hospitalized for initial treatment because of the moderate to advanced states of ketosis frequently found at the time the diagnosis is suspected Such measures are usually unnecessary in most cases of adult diabetes who apparently withstand glycosuria for long periods of time without developing ketosis

5 The associated *degenerative vascular changes* characteristic of diabetes which in adult patients may be evident at the onset or appear within a short time are absent initially in the juvenile diabetic With long duration of the disease however these changes appear prematurely and inevitably as diabetic children survive to adulthood

6 Episodes of *ketosis acidosis and coma* occur more frequently and precipitously in diabetic children because of the marked instability of the liver glycogen stores in young individuals The increased incidence of intercurrent infections in childhood and the adverse influence of severe emotional disturbances intensify the susceptibility to ketosis In view of the meager carbohydrate reserves in diabetic children during ketosis and coma the administration of parenteral glucose becomes imperative in the treatment of the latter condition

7 The *caloric requirements* of diabetic children are greater than those of adult patients particularly in view of the specific needs for *growth* and *development* Treatment by dietary restriction so often successful in adult patients, cannot meet these demands and in the early insulin era led to

and repeated at four hour intervals until acetonuria disappears. Additional carbohydrate usually in the form of fruit juice should supplement each dose of insulin.

III. TREATMENT OF ACUTE MEDICAL AND SURGICAL COMPLICATIONS

Infections.—Insulin, adequate nutrition and chemotherapy have removed the traditional fear of infections in the *treated* diabetic patient, except where circulatory impairment exists as an insurmountable obstacle. To regard the treated diabetic individual as being especially susceptible to infections is unjustified in the light of current knowledge. In former years *acute pneumococcus mastoiditis and lung abscess* seemed to be more frequently associated with diabetes, yet both conditions have virtually disappeared from the diabetic and non-diabetic population. Tuberculosis, which before the discovery of insulin was present in almost one-half of all fatal cases, now is found no more frequently in diabetes than generally.[8] In fact, a chest survey of the diabetic patients attending the clinic at our hospital revealed more unsuspected pulmonary neoplasms than tuberculosis on x-ray. *Infections complicate diabetes by imposing a catabolic state upon a metabolic balance which may in itself further intensify the catabolic processes because of increased insulin needs.* The combination of infection *and* ketosis is the reason for general concern.

Treatment of the infection differs in no way from that in a non-diabetic individual. The normal response to chemotherapy by infections of the skin, urinary and pulmonary tract can be obtained with the usual dosage of *sulfonamide, penicillin, aureomycin, etc.* when the diabetes is managed adequately. The latter requires the intake and *utilization* of a minimum of 150 to 200 grams of carbohydrate. If possible, the patient should consume his regular diet. In the presence of anorexia, however, this amount of carbohydrate must be provided in liquid form for oral administration and by the intravenous route in case of vomiting (1500 to 2000 cc. of 10 per cent glucose in water). Urinalysis for glucose and acetone should be performed *at least 3 times a day, and in ketosis every four hours preferably.*

Insulin is indicated in the *mild* case previously treated without it, when glycosuria appears in more than trace amounts. Ordinarily 10 units of regular insulin may be given before each meal depending upon the presence or absence of more than minimal glycosuria at that time. Naturally, 20 unit doses will be employed if 4 plus glycosuria persists throughout the day. The appearance of acetonuria without glycosuria represents a *starvation ketosis* and *indicates the need for additional carbohydrate rather than more insulin.* If parenteral glucose administration becomes necessary, it is safer to await the results of fractional urinalysis before giving insulin to these patients. The usual practice of prescribing 1 unit of insulin for every 2 grams of glucose administered or excreted has no physiologic validity, and in mild diabetes any such formula might provoke hypoglycemia, the slow drip of intravenous glucose solution notwithstanding.

The patient already receiving insulin should *maintain his basic dose* with additions of rapidly acting regular insulin in doses of 10 to 20 units before

had originally been expected.[104] My observations[6] revealed diabetic retinopathy in every instance within a twenty-five year duration of the disease. This has now been confirmed by others.[107, 102] White[102] in a survey of 200 juvenile patients surviving twenty years of diabetes found vascular damage in 92 per cent, while Chute,[103] in a smaller group with similar duration, noted it in 80 per cent. The most dismal report that of Lancoln's Clinic[101] concludes that "sixteen years after the commencement of diabetes no patient is free from nephropathy; after twenty-one years not a single patient is still alive." A tour of the continent of Europe failed to reveal a single case entitled to a victory medal for having lived with diabetes for twenty-five years without evidences of vascular damage according to Joslin.[105] Despite the inexorable development of premature degenerative changes in many juvenile diabetic patients, now adult men and women are able to carry on an active and productive existence.

Treatment of Juvenile Diabetes.—The objectives of treatment outlined for the adult patient apply equally well to children. Examples of the higher caloric requirements of the latter, according to the National Research Council, include 2000 calories for age seven to nine years, 2500 calories for age ten to twelve years, 3200 calories for age thirteen to fifteen years, and 3800 calories for age sixteen to twenty years. Glycosuria is even less significant as a criterion of management than in the average adult for the reasons outlined above. Growth and development are the major indications of the adequacy of treatment.

Initial treatment in younger children is usually performed in the hospital because ketosis often is the presenting condition at the onset. In the absence of clinical acidosis the ambulatory treatment follows the pattern described on page 1010 except for the use of smaller doses of insulin. Ten units of both regular and protamine zinc insulin should be administered separately. The normal diet to which the child is accustomed is permitted except for the omission of sugar, syrups and pastry. As indicated by acetonuria or excessive glycosuria with persistent symptoms, a similar dose of regular insulin may be repeated before each meal the first day. By the second day a 2:1 mixture, NPH, or globin insulin should be employed for permanent treatment since protamine zinc insulin alone is rarely applicable to the peculiar requirements of childhood diabetes. The dose of insulin must be gauged according to the reduction or absence of early morning glycosuria and the freedom from acetonuria and hypoglycemia. Adjustments of the proportions of rapid and slow acting insulin effect in a mixture are made on a similar basis. Increments of 2 units are sufficient for the average young child while adolescent patients usually require increases of 5 to 10 units like adults. Some of the highest insulin requirements obtain during adolescence with an average of 60 to 70 units, according to the general experience.[95] Stabilization is not to be expected because of the ever changing physical status evidenced by growth, the impact of puberty and adolescence, and the inherent lability of juvenile diabetes.

The significance of *acetonuria* during illness and periods of emotional tension should be imparted to the patient and the parents. On finding acetone by the simple tests now available, an additional dose of *regular* insulin (equal to 20 per cent of the total daily amount) should be taken

initiated preoperatively along with regular insulin in an amount equal to one-third the known total daily requirement for each 1000 cc of solution

Preoperative preparation for *emergency* surgery of a major degree depends on the condition of the patient and his previous diabetic status If nutrition has been adequate and ketosis is absent intravenous glucose and insulin in the manner above may be instituted The coexistence of moderate ketosis warrants more vigorous treatment as outlined below

Minor surgery ordinarily requires no alternation in the customary regimen of the patient

Postoperative treatment must provide 150 to 200 grams of carbohydrate per day The infusion which was begun before or during operation is continued until the patient is able to take liquid nourishment adequately Fifty grams of glucose should be given in the form of a 5 per cent solution in normal saline in order to maintain the salt requirement while the remaining 100 to 150 grams of glucose can be administered in a 10 per cent solution in water Until fractional (four hourly) urine collections are available it is wise to follow the preoperative routine of giving one third of the total daily insulin requirement in the form of regular insulin for every 50 grams of glucose As urine specimens become available regular insulin may be prescribed according to the degree of glycosuria and acetonuria in 10 to 20 unit doses Once the patient is able to take nourishment by mouth one half the basic insulin dose may be reinstituted the day after operation with occasional supplements of regular insulin during the day as needed The usual insulin dose can be employed by the second or third day when the diet also approaches the normal

As tolerance improves and ambulation of the patient is encouraged the postoperative period is fraught with the hazard of hypoglycemia unless the insulin dose is adjusted to allow for this eventuality A more rapid decrease in the insulin dosage is often necessary following the sudden removal of a gangrenous extremity or the evacuation of a suppurative focus

DIABETIC KETOSIS ACIDOSIS AND COMA

The pathologic physiology of diabetic ketosis acidosis and coma as described in detail in chapter 31 serves as the basis for the discussion which follows *Insulin insufficiency is the cause of diabetic ketosis regardless of the mechanism responsible for its increased need* The usual precipitating factors include infection physical and emotional trauma and starvation or vomiting (which favor protein catabolism in the absence of adequate carbohydrate intake) as well as actual insulin deficit through the omission or reduction of the necessary dose An old concept that excessive carbohydrate ingestion also led to ketosis has now been generally discarded

Ketosis —Mild to moderate ketosis may be treated adequately at home in the absence of complications requiring hospitalization Symptoms of excessive thirst polyuria and malaise represent a fairly rapidly reversible state with simple adequate ambulatory treatment The appearance of intense nausea vomiting somnolence and hyperpnea indicate the need for hospital treatment

each meal depending on the severity of glycosuria and the appearance of acetonuria in the fractional specimens. In relatively mild illness such as upper respiratory infections, the basic insulin dose may be adequate in preventing excessive glycosuria or the development of acetonuria without recourse to the more intense program outlined above. The course of treatment should be modified on the basis of clinical evaluation of the nature of the infection and the character of each patients' diabetic state including his responsiveness to insulin, and his resistance to ketosis. If the patient is unable to eat, the basic dose of slow acting insulin should be cut in half and supplements of regular insulin in 10 to 20 unit doses given with the view towards maintaining some glycosuria without acetonuria in the fractional specimens. This regimen is also to be followed when parenteral glucose administration is resorted to. Even larger doses of regular insulin 30 to 50 units or more may be needed in patients with ordinarily high insulin requirements or in the presence of severe toxemia. Resolution of the infection calls for close attention to the possibility of rapidly diminishing insulin requirements lest hypoglycemia ensue, particularly when the patient becomes ambulatory during convalescence.

Surgery and Anesthesia.—Just as the attitude towards infection in diabetes has been altered favorably in recent years by medicine's capacity to maintain normal nutrition and resistance through the use of insulin and chemotherapy, so has the ability of the diabetic patient to withstand elective and emergency surgery been improved. With adequate insulin, fluid and carbohydrate replacement possible within a matter of hours the surgeon need not, in the face of urgently needed intervention, wait for the diabetes to be straightened out as in former years. Except for cases of diabetic coma it is possible to prepare the average surgically emergent diabetic patient within the time ordinarily required for non-diabetic patients.

Anesthesia offers some difficulty in the management of diabetes not only because of possible liver damage on the basis of toxicity and anoxia but in addition the postoperative vomiting and nausea induces or aggravates ketosis. The anesthesia of choice is either local block or spinal anesthesia. Of the general anesthetic agents nitrous oxide, sodium pentothal intravenously, cyclopropane and ethylene are favored in their respective order. Ether and chloroform are to be avoided whenever possible.

Preoperative preparation for major *elective* surgery requires the maintenance of normal nutrition by continuing the usual diet insulin regimen of of the patient until the day of operation. On the morning of that date it is best to omit the customary dose of slow acting insulin because of the possibility of hypoglycemia. The latter is not uncommon in ordinary experience when either a light breakfast no lunch order is prescribed for an afternoon surgical procedure or when this is scheduled for the morning breakfast is omitted. Recourse to regular insulin is preferable during the day of operation. A dose of regular insulin one third the basic total amount is given if glycosuria is present in more than traces on the morning of operation, otherwise it may be omitted pending the result of postoperative urinalysis. If fasting be prolonged because of a delay in the operating schedule a slow intravenous infusion of 10 per cent glucose should be

1 the duration of coma
2 the degree of unconsciousness
3 the age of the patient
4 his cardiovascular status
5 the presence of complications which either influence diabetes adversely or are fatal *per se* and least important of all
6 the degree of acidosis

A clinical evaluation along these lines is essential in every instance of diabetic coma in order to individualize the treatment Thus a preceding history of prolonged vomiting and diarrhea indicates a profound loss of base which cannot be compensated for by removal of the ketone acids alone

General Rules of Treatment — The following general rules are vitally necessary for proper treatment

1 *Immediate hospitalization*

2 *Immediate and continuous treatment* begun before or *en route* to the hospital

3 *Constant supervision by the attending physician and nursing personnel* The presence of the physician is required until clinical and chemical evidences of ketosis have disappeared completely Otherwise the treatment may be compared to a major surgical procedure wherein the attending surgeon departs after making the initial incision leaving verbal orders for the completion of the operation

Aims of Treatment — The *specific physiologic* aims of treatment are

1 To inhibit the formation of the ketone bodies by the administration of *insulin* and *carbohydrate*

2 To accelerate the excretion of the ketone bodies by restoring the *water* deficit and

3 To replace the depleted stores of electrolytes particularly *sodium chloride*

Essentials of Treatment —In order to accomplish these goals the following *therapeutic program* is required

1 *Specifically essential*
  a) *insulin* (rapid acting regular insulin only)
  b) *fluids*—6000 to 7000 cc
  c) *sodium chloride*—approximately 26 grams
  d) *glucose*—approximately 300 grams
2 *Generally essential*
  a) chemotherapy routinely on admission
  b) whole blood or plasma transfusions in peripheral circulatory collapse
  c) warmth and rest
  d) catheterization emptying the bladder then leaving the catheter indwelling so as to facilitate repeated frequent urine collection
  e) vitamin B complex and ascorbic acid
3 *Occasionally essential*
  a) parenteral alkali administration lactate or bicarbonate
  b) gastric lavage alone or followed by the instillation of bicarbonate
  c) parenteral administration of potassium

The home care of ketosis requires frequent telephonic communications between patient and physician. Self treatment consists in

1. Rest and the avoidance of physical effort
2. Analysis of every urine voided for glucose and acetone
3. Immediate administration of 30 to 40 units of regular insulin in the case of severe diabetes and half as much in milder instances
4. Drinking 1 glass of fruit juice or tea sweetened with 3 teaspoons of sugar every one or two hours
5. Repetition of the original dose of regular insulin at intervals of two to three hours until acetonuria disappears. At this time the ingestion of juice may be discontinued and a normal meal schedule followed. Excessive glycosuria or persistent symptoms without acetonuria warrant the continuation of the regular insulin in half the earlier dose at the same intervals

Diabetic Acidosis and Coma.—A rapid transition to the more advanced stages of ketosis yields the clinical picture of acidosis and finally coma. Lethargy, semi-consciousness or stupor, intense dehydration, circulatory collapse, and air hunger characterize this state. A beefy dry tongue, soft eyeballs and a loss of tissue turgor indicate the severity of dehydration. A dry pleuritic friction rub such as has been observed in the dehydration of cholera may be noted. Circulatory collapse is evident in the rapid thready pulse, falling blood pressure, subnormal temperature, cold dry extremities, and stupor, as well as oliguria and anuria in the extreme case. Vomiting, abdominal pain and tenderness and leucocytosis suggest an acute surgical abdomen.

The *diagnosis* of severe diabetic acidosis and coma can be made with little hesitation on the basis of the history and typical clinical picture. Confirmation may be obtained rapidly by the finding of 4 plus glucose, acetone and diacetic acid in the urine. This data and the marked acetone odor to the breath suffice to initiate treatment at once without waiting for blood sugar or plasma CO_2 combining power determinations. If fact, the degree of abnormality obtained in the latter chemical observations cannot be correlated with the severity of diabetic coma. Thus mild to extreme hyperglycemia (200 to 1500 mg. per cent) may be found in this state, while consciousness may be retained with a plasma CO_2 combining power of 4 volumes per cent, hyperpnea being the only clinical expression of this extremely subnormal value. Ketonemia and circulatory collapse, however, are related to the depth of coma.

Hypoglycemic insulin reactions are easily differentiated on the basis of the sudden history, the moist skin and the absence of dehydration, Kussmaul breathing and acetone odor to the breath. Although glycosuria may be found in this state, acetone and diacetic acid will be lacking in the urine. When in doubt, the therapeutic response to intravenous glucose administration may be resorted to.

TREATMENT OF DIABETIC COMA

Factors Determining Prognosis of Treatment.—The factors which determine the outcome of treatment in diabetic coma are

of intense dehydration The rate of absorption of the subcutaneous fluid from the local injection site also serves as an index of circulatory integrity varying directly with the latter

Subsequent Treatment — The subsequent treatment will be determined by the clinical and chemical response

2 hours after admission give 100 units of regular insulin subcutaneously

4 hours after admission

1) give 50 units of regular insulin subcutaneously if there is evidence of improvement in the clinical picture the fluid balance and beginning diminution in urinary diacetic acid content This point in time determines the degree of insulin resistance which may exist 300 units of insulin having been given already some response in any of the clinical findings or in the second blood sugar determination if available justifies a progressively decreasing insulin dosage in the subsequent hours A lack of response in either of these 2 criteria indicates the need for more intensive insulin therapy In this instance 100 to 200 units may now be given depending upon these indications and the dose repeated at hourly intervals or increased even further if need be This is also the time of decision as to the need for alkali
2) if the CO_2 combining power remains below 15 volumes per cent or severe hyperpnea is unimproved at this time give 500 cc of 5 per cent sodium bicarbonate intravenously slowly
3) add 5 cc of parenteral vitamin B complex solution and 200 mg of ascorbic acid to the infusion and repeat in twelve to twenty four hours

6 hours after admission

1) *slow* the *infusion* to 120 cc per hour
2) give 25 *units* of regular insulin if a favorable response continues and *repeat every two hours* until acetonuria disappears

9 to 10 hours after admission

1) the patient having received 3 liters of saline by this time the infusion is changed to 10 per cent glucose in distilled water This prevents excessive salt retention and provides more glucose for the coming period of greater insulin efficiency

12 hours after admission

1) this is the critical point at which *hypopotassemia* develops Watch for it clinically and by ECG If the patient is able to take orange juice and broth he will obtain potassium in moderate amounts In the lack of chemical confirmation of hypopotassemia any clinical suspicions of the condition may be safely treated by the slow intravenous administration of 1 gram of potassium chloride every hour for 4 doses If the patient is able to tolerate fluids by mouth the 4 grams may be given orally within a two hour period A glassful either of orange juice chicken broth or milk supplies almost one half a gram of potassium chloride
2) both the insulin dose and its frequency of administration should be decreased depending on the urinary glucose and ketone content
3) watch for hypoglycemia

Guides to the Efficacy of Treatment — The *effectiveness* of *treatment* and the indications for its modification are gauged by the following criteria

1 *The clinical picture*

a) hyperpnea diminishes directly with improvement in the degree of acidosis

b) restoration of consciousness is related to improvement in ketonemia

c) return of tissue turgor and normal ocular tension indicate fluid retention

d) disappearance of nausea and vomiting is a favorable sign which permits oral fluid administration

2 The *urinary output* and *blood pressure* determined at *hourly* intervals as indications of impending circulatory collapse which may require whole blood or plasma transfusion

3 The *fluid balance* as a measurement of adequate fluid retention

4 The *urinary acetone* and *diacetic acid* content primarily and *glycosuria* secondarily determined first at hourly then at two hourly intervals until the ketone bodies disappear

5 The blood sugar level and the plasma CO_2 combining power determined initially and about four to six hours later Although highly desirable these tests are not absolutely essential the management of a case of severe acidosis or coma can be accomplished quite satisfactorily with limited biochemical facilities in the presence of good clinical judgment and urinalyses

Initial Treatment —The *initial treatment* of a typical case of diabetic coma consists of the following procedures

1 The patient is put to bed and covered with warm blankets hot water bottles being avoided

2 The bladder is emptied and an indwelling catheter inserted the urine specimen being saved for analysis

3 200 *units of regular insulin* are administered subcutaneously In the presence of peripheral circulatory collapse this may be divided 100 units being administered intravenously and the other 100 units subcutaneously

4 Blood samples are drawn

5 A *continuous intravenous infusion* of 5 per cent glucose in normal saline is begun flowing at a rate of 500 cc during the first hour and 250 cc an hour thereafter

6 600 000 units of procaine penicillin (aqueous suspension) are injected intramuscularly

7 Whole blood or plasma transfusion is given if peripheral circulatory collapse is evident on the basis of an abnormally low blood pressure level or a decreasing urinary output approaching anuria

8 Gastric lavage is indicated only when vomiting is persistent It is rarely necessary inasmuch as vomiting ceases when nothing is given by mouth Furthermore the use of lavage removes invaluable electrolytes which, if left within the stomach would be reabsorbed

9 A subcutaneous clysis of 1000 cc of normal saline may be indicated in addition to its simultaneous intravenous administration in the presence

low 15 volumes per cent) in the presence of decreasing glycosuria or hyperglycemia justify the administration of 500 cc of sodium bicarbonate in 5 per cent solution given slowly by the intravenous route The response to one-sixth molar sodium lactate (Hartmann s) solution in such severe acidosis is neither as rapid nor as effective If any improvement in the acidotic state is being manifested clinically or chemically then the use of sodium lactate offers no immediate advantage since an adequate reserve of base is obviously becoming available with the decrease in the organic keto-acids

Potassium —Potassium deficiency is one of the possible sequelae of treatment A high serum potassium level obtains initially during diabetic coma falling between 12 to 24 hours after therapy has begun then rising gradually

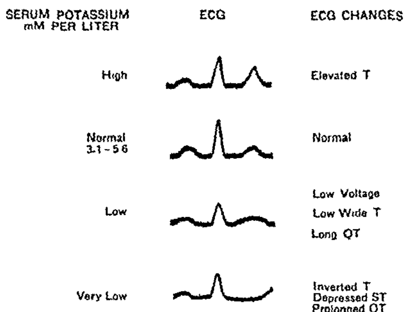


Fig 88 —Diagramatic Representation of the Electrocardiographic Changes Associated with Alteration in Serum Potassium Concentration

over a period of several days before reaching normal values The initial administration of potassium early in the treatment of diabetic coma is unjustified and hazardous in view of the high level at that time and possible simultaneous impairment of kidney function Furthermore the toxicity of an increase serum potassium level is enhanced in the presence of the low sodium levels which develop during diabetic coma

The clinical syndrome of hypopotassemia which may appear 12 to 24 hours after the *initiation of treatment for* diabetic acidosis is characterized by restlessness disorientation muscular weakness and respiratory difficulty Breathing is shallow and rapid and accomplished in large part by the accessory muscles of respiration Death may occur from either respir

4) begin the oral administration of 120 cc of orange juice, broth, coca cola or ginger ale every hour, if tolerated without vomiting

24 hours after admission

1) the patient can usually tolerate a soft otherwise normal diet
2) the infusion is discontinued and the catheter withdrawn at this time or before, if possible
3) a basic dose of the patient's usual slow acting insulin should be given in one half his customary dose
4) supplemental regular insulin may be required as described in the treatment of ketosis
5) repeat the penicillin injection as prophylaxis

48 hours after admission

1) return to the regular diet
2) adjust the insulin dose accordingly

The above outline of a typical case excludes consideration of the many variables in the actual treatment of patients. Proportionately less insulin and fluids would be needed for a case of moderate acidosis. *Children* in diabetic coma require doses of only 10 to 20 units given at half to one hour intervals while their base and carbohydrate deficits are relatively greater than adults. Consequently pediatricians resort to the use of alkali more often than do internists. The parenteral fluid replacement needed in the first 24 hours in diabetic children amounts to 10 to 15 per cent of the body weight.

Insulin.—Instead of repeated injections of 25 to 50 unit doses during the early hours of treatment, it would seem more logical to administer an initial dose equal to about half the anticipated total requirement (450 to 500 units in the first 24 hours on the average). This insures more immediate as well as more adequate insulin effectiveness in reversing the catabolic state. A lack of responsiveness to insulin is not uncommonly found in diabetic coma and the use of a thousand or more units is not unusual.

Fluids and Salt.—Although the average *fluid deficit* in coma amounts to about 6000 cc, it should not be supplied as saline alone. With the administration of 3 liters of normal saline, the average *sodium chloride deficit* of 26 *grams* has been replenished and the remainder of the parenteral fluid must be limited to glucose in distilled water. Hypochloremic anuria requires the intravenous administration of 50 cc of 10 per cent sodium chloride solution.

Glucose.—Glucose as a 5 per cent solution in normal saline should be used during the initial treatment of diabetic acidosis because one fourth of all cases of diabetic coma do not present a marked initial hyperglycemia (being under 300 mg per cent in fact). After sufficient saline has been provided, a 10 per cent solution of glucose in distilled water must be made available for the correction of ketosis. It also serves as a buffer against the cumulative hypoglycemic effects of the large amounts of insulin used in treatment. Naturally, the administration of fruit juices by mouth is desirable as early as possible, not only as an abundant source of carbohydrate but of potassium as well.

Alkali.—Alkali is rarely needed except in the case of a severe deficit of base due to protracted vomiting and diarrhea. In such patients persistent hypernea and unyielding acidosis (with CO_2 combining power remaining be-

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atory or circulatory failure. The diagnosis may be confirmed by finding a diminished serum potassium concentration (below 2.5 milliequivalents per liter).

Certain electrocardiographic changes are consistent with this state and are characterized by a marked prolongation of the Q-T interval and a flattened T wave (Fig 88). The latter becomes exceedingly elevated during potassium intoxication, an equally lethal chemical state, especially in the presence of impaired renal function.

The indications for potassium therapy should be based on the close clinical observation of each individual case during the critical 12 to 24 hour period of treatment. Just as the dose of insulin needed to overcome diabetic coma is extremely variable, so the amount of potassium indicated in any case is equally unpredictable.

With respect to the replacement of the other electrolytes such as phosphate, magnesium, etc., there is even less unanimity of opinion than exists in the case of potassium. On the basis of the metabolic data available, the treatment of diabetic coma at present cannot be reduced to a fixed formula for fluid and electrolyte replacement in any specific instance.

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4 *Disturbances of hormonal regulation*
   a Adrenal cortical insufficiency
   b Pituitary (adenohypophyseal) hypofunction
   c Hypothyroidism
5 Disturbances of the central nervous system
   a Hypothalamic diencephalic and brain stem lesions
6 Exaggerated response to alimentary hyperglycemia (rapid intestinal absorption)
   a Post gastroenterostomy   b Post gastrectomy (partial or total)
7 Autonomic nervous system imbalance—functional hypoglycemia
   a Idiopathic hypoglycemia of infants and children
   b Autonomic nervous system instability or psychosomatic fatigue
   c Functional hypoglycemia in response to the normal postprandial hyperglycemia
8 Increased insulin secretion—organic hyperinsulinism
   a Pancreatic islet cell adenoma
   b Pancreatic islet cell carcinoma
   c Adenomatosis or generalized hyperplasia and hypertrophy of the islets of Langerhans
9 Factitious (surreptitious insulin administration)

SYMPTOMS AND SIGNS

The symptoms and signs of spontaneous hypoglycemia are identical with those of insulin induced hypoglycemia which have been described in detail in the chapter on the Treatment of Diabetes Mellitus. In brief they represent combinations of vasomotor motor and psychic responses. Initially general weakness and faintness tremulousness pallor sweating hot and cold flushes and palpitation are soon followed by hunger pains visual disturbances such as diplopia tingling of the lips and tongue and vague restlessness. As hypoglycemia continues or increases in severity mental confusion disorientation severe headache personality and behavioristic changes vomiting delirium mania or apathy and somnolence set in leading finally to convulsions and deep coma.

The rapid dramatic response to sugar or if need be to intravenous glucose administration is a therapeutic test of the diagnosis.

The severity of the clinical picture is no index of the underlying cause since even patients with functional hypoglycemia can present all the above. The blood sugar level at which convulsions or serious symptoms develop may differ in different individuals depending upon the etiology of the hypoglycemia. Patients with disease of the central nervous system Addison's disease or pituitary insufficiency may present striking symptoms at blood sugar levels of 60 mg per cent while patients receiving insulin shock therapy for psychotic states may show very little disturbance with blood sugar levels of 20 mg per cent. The early premonitory symptoms may be absent or unnoticed so that the first manifestation of hypoglycemia may be a severe personality disorder or convulsions. Consequently patients with this syndrome are not infrequently admitted to hospitals with erroneous diag

Chapter 34

SPONTANEOUS HYPOGLYCEMIA AND HYPERINSULINISM

By Henry Dolger, M.D.

The first clinical observation of hypoglycemia was made in patients with Addison's disease[1] in 1910. Soon after the discovery of insulin, Harris[2] in 1923 created the concept and term hyperinsulinism. The finding of an insulin producing carcinoma of the islets of Langerhans by Wilder and his associates[3] in 1927 and the first report[4] two years later of a dramatic cure in a patient with hyperinsulinism following excision of a benign adenoma of the islet cells spurred wide interest in the subject. The expanding diagnostic awareness of spontaneous hypoglycemia unfortunately outdistanced the critical analysis of the multiple etiologic factors and in an enthusiastic search for the syndrome the terms "hyperinsulinism" and "spontaneous hypoglycemia" were accepted as synonymous. Whipple[5] and Conn[6] were responsible for resolving the confusion, the former by establishing the sharp criteria for hyperinsulinism and the latter by the clean-cut differentiation of functional and hepatogenic hypoglycemia from organic hyperinsulinism.

The consideration of the pathogenesis of hypoglycemia must include all the systems responsible for the maintenance of the normal blood sugar level. The functional integration of the islets of Langerhans, the pituitary, thyroid and adrenal glands, the liver and the autonomic and central nervous systems is required for this purpose. Differentiation of spontaneous hypoglycemia on a physiologic basis will not only aid in correct diagnosis but will indicate the rational of appropriate treatment.

ETIOLOGIC PHYSIOLOGY OF SPONTANEOUS HYPOGLYCEMIA

1. Utilization of blood sugar faster than it can be supplied
   - *a* Severe continuous muscular exertion
2. Inadequate glycogen reserves
   - *a* Severe inanition
   - *b* Renal glycosuria
3. Failure of intrinsic hepatic mechanisms for storage, synthesis or secretion of glucose
   - *a* Toxic hepatitis
   - *b* Acute ascending infectious cholangiolitis
   - *c* Diffuse carcinomatosis
   - *d* Fatty degeneration
   - *e* Glycogenosis (von Gierke's disease)
   - *f* Post-operative hypoglycemia

THE DIAGNOSIS AND MANAGEMENT OF THE VARIOUS FORMS OF SPONTANEOUS HYPOGLYCEMIA

1 **Severe Continuous Muscular Exertion** — Normally two hours of vigorous exercise have no significant influence[24] in reducing the fasting blood sugar level and may in fact cause it to increase[24] However if the exertion is unusually prolonged as in a marathon race hypoglycemia may supervene in some instances the clinical picture of shock being associated with blood sugar levels of 50 mg per cent or less[25] Such effort hypoglycemia is usually limited to individuals with autonomic nervous system instability[4] Severe exertion will precipitate or aggravate hypoglycemia in patients with organic hyperinsulinism impaired liver function inadequate glycogen reserves or certain endocrine diseases Therefore such patients should be advised to guard against unusual muscular effort during any period of fasting

2 **Inadequate Glycogen Reserves—Severe Inanition.** — The glycogen reserves of the liver in the normal adult can be depleted by starvation to the point where gluconeogenesis from tissue proteins may be inadequate to maintain normoglycemia This is especially true of infants in whom hepatic glycogen stores are more labile and more easily exhausted than in adults thereby explaining the ease and intensity with which the former develop hypoglycemia upon starvation A normal young woman on a voluntary fast for five days developed intense symptoms of hypoglycemia by the fifth day when the blood sugar level had fallen to 45 mg per cent In a series of normal subjects starved for two weeks the blood sugar fell after the second day and reached hypoglycemic levels with clinical manifestations by the end of the first week[28]

The prolonged undernutrition which prevailed in France during the years 1941-42 led to a number of instances of spontaneous hypoglycemia in persons whose diets were deficient mainly in protein and fat[9] Typical collapse with blood sugar levels below 40 mg per cent was noted in these cases and a rapid response followed the intravenous administration of glucose Of interest were the findings of hypophyseal atrophy and lesions in the diencephalon in the fatal cases

Terminal hypoglycemia may occur in cachetic states The starvation treatment of diabetes mellitus popular in the pre-insulin era occasionally induced severe hypoglycemia In 1921 Joslin[30] reported 3 such instances wherein vigorous undernutrition effected an abrupt change from diabetic acidosis (which already had depleted the hepatic glycogen stores) to fatal hypoglycemia—1 patient succumbing with a blood sugar level of 40 mg per cent one week after admission with a blood sugar level of 360 mg per cent Cachexia in diabetic patients being treated with insulin has been known to lead to hypoglycemia long after the insulin has been discontinued In one such patient dying in hypoglycemia one week after the cessation of insulin therapy complete atrophy of the pancreas was found without a single islet of Langerhans demonstrable[31]

Maltreatment by severe carbohydrate restriction of patients with renal glycosuria can provoke hypoglycemia as the hepatic glycogen reserves

noses, such as psychosis, brain tumor, epilepsy, acute alcoholism, or cerebral vascular accident Psychoneurosis hysteria and peptic ulcer may be suggested by the milder symptoms

NEUROLOGIC SEQUELAE

The widespread cerebral damage in fatal hypoglycemia has been the subject of numerous reports [7, 8, 9] Recovery from prolonged hypoglycemia with residual impairment of cerebral function has been recognized as post hypoglycemic encephalopathy [10] More recently instances of pancreatic islet cell adenoma have been reported with peripheral nerve and spinal cord damage causing foot drop [11] atrophy of the muscles of the hand and calf [1] and lesions in the posterior columns anterior horn and pyramidal tracts [13] These changes followed an unfortunate delay in surgical treatment One child supposedly developed marked internal hydrocephalus on the basis of repeated episodes of severe spontaneous hypoglycemia [14]

DIAGNOSTIC PROCEDURES IN HYPOGLYCEMIA

1 History of attacks with definite symptom pattern coming on during the fasting state 2 Fasting blood sugar levels of 50 mg per cent or less 3 Immediate recovery upon the administration of glucose	Whipple's[5] triad for organic hyperinsulinism
4 History of previous good health 5 Intolerance to fasting	Wilder's[15] addition to the triad

6 Glucose tolerance —Conn's[6] differential by typically distinct patterns for functional alimentary and hepatogenic hypoglycemia as well as for organic hyperinsulinism

7 Insulin tolerance —*a* Fraser *et al* [16] reported a delayed recovery of blood sugar level following 5 units of regular insulin I V in cases of organic hyperinsulinism
b Maranon[17] noted marked sensitivity to the insulin test in Addison's disease and danger in its use

8 Electroencephalographic changes during hypoglycemia —restored to normal by glucose (Himwich) *et al* [18]

9 Liver function studies and cholecystography —abnormal in hepatogenic hypoglycemia (Conn[6])

10 Blood sugar response to epinephrine —decreased in hepatogenic hypoglycemia (Conn[43])

11 Demonstration of pituitary and adrenal sufficiency —eosinophil response to epinephrine and ACTH (Thorn and Forsham[19])

12 BMR for hypothyroidism (Tedstrom[20])

diagnosis of hepatogenic hypoglycemia lies in the fact that its treatment is the direct opposite of that for functional hypoglycemia. Whereas patients with the latter benefit by carbohydrate restriction, the *therapy* of hepatogenic hypoglycemia calls for a *high carbohydrate* (100 to 500 grams) *high protein* (120 grams) diet with a night meal on retiring. There should be no long intervals between feedings.

The type of hepatogenic hypoglycemia which offers the most dramatic therapeutic response is that due to an ascending infectious cholangiolitis. Operative treatment of the underlying disease results in the restoration of the normal blood sugar level in addition to recovery of the impaired associated disturbances of liver function. The following abstract of Conn's[43] first case provides a classical illustration of such metabolic alterations.

Illustrative Case

A forty-seven year old man presented a one-year history of attacks of unconsciousness between the hours of 3 and 7 A.M. occurring several times a month. Excessive sweating, disorientation, vomiting and incontinence of urine and feces were associated symptoms, but convulsions were not noted. Recovery from the attacks was gradual with complete amnesia for the episode. Eating had been found to terminate the attacks rapidly. On one occasion intravenous glucose administration effected prompt recovery. There never had been any symptoms referable either to the gall bladder or liver.

Physical examination was negative. Liver function studies were abnormal with impaired galactose tolerance, high bromsulphalein retention, macrocytosis and low total serum proteins with inversion of the A/G ratio. Cholecystogram revealed poor visualization of the gall bladder with possible stones.

On a low carbohydrate diet (50 grams) severe hypoglycemia developed every morning with blood sugar values of from 14 to 18 mg. per cent. Glucose tolerance tests showed a high delayed plateau curve rising to 220 mg. per cent and falling to 100 mg. per cent by the third hour. The delayed fall to hypoglycemic levels in the fourth to seventh hours characteristic of hepatogenic hypoglycemia was not observed because the test was terminated in the third hour.

Respiratory data indicated normal glucose oxidation both in the fasting state and after glucose ingestion in contrast to the increased oxidation seen in organic hyperinsulinism. This suggested that fasting hypoglycemia was due to impairment of glycogenesis and possibly glycogenolysis. One cc. of epinephrine resulted in a minimal rise of 10 mg. per cent in the blood sugar level and this drug was ineffective in relieving the attacks.

Exploratory laparotomy revealed the pancreas to be grossly normal, while the liver, although of normal size, appeared pale and nodular. The gall bladder was distended, containing stones and thick pus. Biopsy of the liver showed active chronic cholangiolitis, biliary cirrhosis and fatty infiltration.

Gradual improvement followed cholecystectomy; the attacks disappeared and after nine months the fasting blood sugar levels had reached normal values. All evidences of impaired liver function also disappeared completely. At this time the glucose tolerance curve was normal although low, and the response to epinephrine was likewise normal (with a rise in blood sugar level of 80 mg. per cent).

4. Disturbances of Hormonal Regulation.—The hypoglycemia associated with hypofunction of the pituitary, adrenal and thyroid glands is presented elsewhere in this volume. Some pertinent items may be mentioned here. Of interest is the historical priority of the first diagnoses of spontaneous hypoglycemia in Addison's disease by Porges[1] (1910) and in pituitary chromophobe adenoma by Cushing (1912). The association of

without repletion from the diet succumb to the unchecked loss of glucose through the urine

3 **Failure of the Intrinsic Hepatic Mechanisms for Storage, Synthesis or Secretion of Glucose** — The importance of the liver in preventing hypoglycemia was established in 1922 by Mann and McGath[3] and its role in regulation of the blood sugar level was further clarified by Soskin Mann and their associates[33] Hypoglycemia has been noted in cases of severe diffuse hepatic degeneration or destruction as in acute yellow atrophy[34] poisoning by chloroform[35] phosphorus[36] and arsenicals,[37] infectious hepatitis[38] advanced cirrhosis,[39] diffuse carcinomatosis[40] and fatty degeneration[41] or metamorphosis[4] Two additions to this list deserve special mention and discussion—acute ascending infectious cholangiolitis[43] and glycogenosis or von Gierke s disease[44]

Hypoglycemia in von Gierke s disease was first described by Snapper and van Creveld[44] The inability to release glucose from the liver glycogen stores in this condition was demonstrated chemically by Schonheimer[45] Unlike the rapid disappearance of glycogen which obtains in the normal postmortem state in von Gierke s disease the glycogen remains unaltered for an unlimited time Although Thannhauser and his associates[47] claimed to have demonstrated a marked deficiency in alkaline phosphatase activity in such livers placing the enzymatic interruption at the point of dephosphorylation of glucose 6-phosphate Wichstein[48] could not support this view since on histochemical analysis he found a normal distribution for both acid and alkaline phosphatase The children with this condition exhibit no rise in blood sugar level in response to epinephrine and are extremely insulin sensitive Despite the extremely low blood sugar levels so characteristic of these patients clinical signs or symptoms of hypoglycemia are manifested rarely

Except for ascending infectious cholangiolitis the clinical picture of the underlying hepatic factor causing hypoglycemia in such patients is quite obvious In addition to laboratory evidence of impaired liver function all patients with *hepatogenic hypoglycemia* exhibit the following diagnostic pattern

1 Fasting hypoglycemia (blood sugar level before breakfast under 50 mg per cent)
2 Intolerance to twenty four hour fast on carbohydrate restriction
3 High prolonged rise (hyperglycemic plateau type) of oral glucose tolerance curve frequently with glycosuria followed by gradual fall to hypoglycemic levels in four to seven hours
4 Little or no significant rise in blood sugar level in response to epinephrine (0 5 to 1 0 cc of 1 1000 solution)

The relation of the attacks to fasting is characteristic occurring most often during the night or early morning just as in organic hyperinsulinism They are infrequent during the day except when meals are omitted

An erroneous diagnosis of diabetes mellitus[43] is not infrequently made in such instances of severe hepatic damage because of the transient glycosuria which follows the abnormal postprandial hyperglycemia due to slow glycogenesis in the liver This may divert the attention of the clinician from the true nature of the disorder[39] The importance of recognizing the

There was a normal rise in blood sugar level in response to epinephrine (from 100 to 199 mg per cent in forty five minutes) Exploration of the pancreas failed to disclose any abnormality and a biopsy of the tail of the pancreas was histologically normal Low carbohydrate diets proved harmful with the attacks becoming more severe and more frequent Carbohydrate feeding every two hours failed to prevent hypoglycemia necessitating the continuous intravenous administration of glucose Two courses of alloxan were given in desperation After the initial one-week course consisting of a total of 3.3 grams of alloxan the fasting blood sugar level rose from an average of 35 mg per cent to 90 mg per cent and all symptoms of hypoglycemia ceased Two weeks later hypoglycemia recurred and a second course of 9 grams of alloxan was given with complete and permanent recovery on a regular diet of 3 meals daily No further episodes were observed and the glucose tolerance test was normal

With subsequent upper respiratory infections and fever convulsions appeared without hypoglycemia The electroencephalogram revealed cerebral dysrhythmia and marked internal hydrocephalus was found on pneumoencephalography

Comment —Darrow's[61] report of the development of spontaneous hypoglycemia *in a child with internal hydrocephalus and other evidences of* cerebral damage suggests the possibility of this mechanism being responsible for the hypoglycemia in this case Recently Talbot[6] has indicated doubt *regarding his original concept that the hydrocephalus was an after* math of idiopathic hypoglycemia and has accepted the possibility of a hypothalamic lesion being the original source of the entire clinical picture *Incidentally, this patient had received ACTH for four days during the* hypoglycemic period with striking improvement in the symptoms and the blood sugar levels Thorn[60] suggested therefore that the adrenal stimulation due to the exploratory operation could have accounted for the amelioration of the hypoglycemia The possible benefit from alloxan therapy suggested by this case and the one reported by Conn and Hinerman[63] is *counter to the experience of other observers all of whom failed to demon* strate any effect of alloxan upon the pancreatic islet cells in man (*see* p 1070)

6 **Exaggerated Response to Alimentary Hyperglycemia** —Rapid intestinal absorption of ingested carbohydrate is inevitable after gastroenterostomy and especially after partial or total gastrectomy This sudden dumping *of each feeding into the small intestine leads to alimentary* hyperglycemia which in turn is followed by marked hypoglycemia Anderson and Long[64] using the isolated perfused pancreas have recently demonstrated the direct effect of hyperglycemia in stimulating the islet cells to secrete insulin Contributing to this phenomenon is the decreased output of glucose by the liver in response to the influx of exogenous sugar—a delicate hepatic *mechanism which Soskin[33] proved so fundamental in blood* sugar regulation A third factor in precipitating rapid hypoglycemia is the accelerated deposition of glucose as glycogen and its increased utilization by the extra hepatic tissues in response to the stimulus of hyperglycemia[65] The entire syndrome can be considered a normal response to an excessive hyperglycemic stimulus (Staub Traugott effect)

The only time these patients exhibit *hypoglycemic symptoms is one to* two hours after meals never on fasting The glucose tolerance curve explains the dynamics of the reaction most clearly with (1) a normal fasting blood

acromegaly[49] with pancreatic islet cell adenomata was reported recently. Whipple[1] noted that in hyperthyroidism associated with pancreatic islet cell tumors, the basal metabolic rate is apt to be deceptively lower than usual. To avoid the possibility of a thyroid storm after removal of the pancreatic tumor he suggests preoperative iodine therapy if the basal metabolic rate is over +15 per cent.

In elucidating the nature of the hypoglycemia in cases of suspected Addison's disease, Thorn and his associates[9] interdict the use of the intravenous glucose tolerance test as a diagnostic aid. In such patients this procedure is fraught with great danger because of a severe hypoglycemic reaction several hours later when the blood sugar level falls precipitously. Spontaneous recovery from this untoward event may be difficult, especially since collapse and coma may supervene. The unusual sensitivity to insulin of the Addisonian patient makes this diagnostic test too hazardous to be used in this condition. This phenomenon was the only clue to the true diagnosis in a case of severe spontaneous hypoglycemia due to extreme bilateral adrenal atrophy.[51] Except for the hypoglycemic symptoms no signs or symptoms of Addison's disease were noted and this diagnosis was unsuspected when the patient was subjected to abdominal exploration for a possible but nonexistent pancreatic tumor. The patient's poor condition during operation prevented resection of the pancreas and death occurred suddenly twenty-four hours postoperatively. The one significant preoperative finding was the development of severe hypoglycemia requiring intravenous glucose therapy following the test dose of 1.7 units of insulin intravenously.

5. **Disturbances of the Central Nervous System.** — Although lesions of the hypothalamus, diencephalon and brain stem have long been associated with the production of hyperglycemia, isolated reports indicate the possibility of such conditions giving rise to hypoglycemia. The latter has been noted following subarachnoid hemorrhage,[52] chronic internal hydrocephalus,[61] general paresis[53] and encephalitis.[54]

When hypothalamic lesions were produced in cats,[55] 80 per cent developed hyperglycemia and the remaining 20 per cent hypoglycemia. The hypoglycemic animals were extremely sensitive to insulin and displayed a decreased hyperglycemic response to epinephrine and to injections of anterior pituitary extracts.[56] Harris believed that some association existed between hypoglycemia and epilepsy,[57] but critical review of his data indicates that he was dealing with hypoglycemic epileptiform seizures. True idiopathic epilepsy is not associated with hypoglycemia.[58]

A report of severe hypoglycemia in an infant subsequently found to have internal hydrocephalus may properly be considered as belonging in this section on *hypothalamic lesions*. *Talbot and his associates*[14] however believe that the hydrocephalus may represent one of the sequelæ of "idiopathic" hypoglycemia.

Illustrative Case

An eight month old baby girl developed hypoglycemic convulsions when five months old. The blood sugar level during a convulsion was 34 mg. per cent. Prompt relief was obtained by intravenous glucose administration.

There was a normal rise in blood sugar level in response to epinephrine (from 100 to 199 mg per cent in forty five minutes) Exploration of the pancreas failed to disclose any abnormality and a biopsy of the tail of the pancreas was histologically normal Low carbohydrate diets proved harmful with the attacks becoming more severe and more frequent Carbohydrate feeding every two hours failed to prevent hypoglycemia necessitating the continuous intravenous administration of glucose Two courses of alloxan were given in desperation After the initial one-week course consisting of a total of 13 grams of alloxan the fasting blood sugar level rose from an average of 35 mg per cent to 90 mg per cent and all symptoms of hypoglycemia ceased Two weeks later hypoglycemia recurred and a second course of 9 grams of alloxan was given with complete and permanent recovery on a regular diet of 3 meals daily No further episodes were observed and the glucose tolerance test was normal

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The only time these patients exhibit hypoglycemic symptoms is one to two hours after meals never on fasting The glucose tolerance curve explains the dynamics of the reaction most clearly with (1) a normal fasting blood

sugar level (2) a rapid rise to hyperglycemic levels within an hour (up to 300 mg per cent) and (3) a precipitous fall to hypoglycemic levels after two hours

Evensen,[66] in a study of the effects of gastric emptying on the glucose tolerance curve following gastric resection or gastroenterostomy, established the preceding criteria for this type of hypoglycemia In addition he proved the nature of its mechanism by duplicating this response in normal individuals given glucose by duodenal tube

The condition is usually unnoticed in the immediate postoperative state when feeding is minimal and frequent Symptoms appear when the patients can eat larger meals on a regular schedule *Treatment* consists in (1) avoiding rapidly absorbed carbohydrate such as fruit juice (2) frequent small feedings of solid or semi-solid foods and (3) a high protein (120 to 150 gm) diet Carbohydrates in the slowly absorbed form of cereal bread and vegetables need not be restricted

Illustrative Case

A sixty two year old man with diabetes mellitus which had been easily managed with 40 units of protamine zinc insulin daily and a normal diet was subjected to total gastrectomy for carcinoma of the cardia During the early postoperative period several daily injections of regular insulin were given according to the usual procedure in the case of the surgical patient with diabetes slow acting protamine zinc insulin being omitted As his condition improved he he was given the customary postgastrectomy feeding of gruel custard and fruit juice The development of typical hypoglycemic symptoms such as weakness sweating and mental clouding about two hour after such feeding was promptly recognized by the patient as insulin shock His vigorous assertions to the effect were disputed by the medical staff who felt secure that the now constant glycosuria proved hypoglycemia unlikely A casual blood sugar determination during one such episode was 52 mg per cent yet one hour before the blood sugar level had been 325 mg per cent

Prolonging the interval between insulin administration and each meal did not arrest the syndrome even with doses as small as 10 units given two hours before meals An attempt at omitting insulin for one day had to be given up because of the rapid onset of severe thirst polyuria and ketonuria by the afternoon A basic dose of 30 units of protamine zinc insulin proved as ineffective as regular insulin in preventing recurrent hypoglycemia in the presence of constant glycosuria Maintaining this insulin dose a change of the diet to one devoid of rapidly absorbed carbohydrate (especially fruit and fruit juice) relieved the patient considerably Division of this otherwise regular diet into 6 equal feedings provided complete relief from hypoglycemia accompanied by a reduction in the amount of glycosuria

Comment —The postgastrectomy syndrome was aggravated by the association of diabetes in this patient Alimentary hyperglycemia was exaggerated further by the usual postprandial hyperglycemia in diabetes producing an extremely high jump-off level for subsequent hypoglycemia The latter developed precipitously in response to the normal mechanism for its production plus the acceleration due to previously administered insulin The abnormally high blood sugar peaks led to almost continuous glycosuria which tended to divert the attention of the medical staff from the consideration of hypoglycemia Frequent small feedings of solid food and the avoidance of rapidly absorbed carbohydrates abolished the hypo-

glycemic attacks and permitted easier regulation of the diabetes with diminution of glycosuria

7 **Autonomic Nervous System Imbalance—Functional Hypoglycemia** —There is a tendency to apply the term functional hypoglycemia to three distinct conditions

a idiopathic hypoglycemia of infants and children

b autonomic nervous system instability or psychosomatic fatigue

c functional hypoglycemia in response to the normal postprandial hyperglycemia

These three comprising the most frequently encountered forms of spontaneous hypoglycemia can be differentiated clinically

a **Idiopathic Hypoglycemia of Infants and Children** —*Spontaneous hypoglycemia may occur in infants and children whose liver glycogen is depleted because of vomiting, diarrhea and exhaustion* The dietary measures so successful in functional hypoglycemia fail in the treatment of recurrent chronic hypoglycemia of the so-called idiopathic type and alloxan[62] subtotal pancreatectomy[64,67] and ACTH[68,69] have been resorted to

Graham and Hartmann[67] reported a case of severe hypoglycemic convulsions in a one-year old infant (with blood sugar levels as low as 18 mg per cent) in whom removal of seven-eighths of the pancreas resulted in recovery The resected gland was histologically normal even as to the size and number of islets of Langerhans The failure of partial pancreatectomy to correct severe chronic hypoglycemia in 2 children led McQuarrie and his associates[68] to investigate the diabetogenic effects of ACTH[69] in counteracting hypoglycemia The following abstract of their report indicates the dramatic effectiveness of ACTH in these 2 children and in 3 cases with less severe hypoglycemia

Illustrative Cases

A one year old infant manifesting frequent and severe hypoglycemic reactions including convulsions had been subjected to partial pancreatectomy with extirpation of about 85 per cent of histologically normal pancreas This procedure resulted in restoration of the fasting blood sugar to normal values with complete relief from hypoglycemic symptoms for about three weeks Then hypoglycemia recurred in a degree of severity almost as marked as before operation

ACTH was administered intramuscularly in doses of 9 mg every six hours over a period of four days Severe hypoglycemia and attendant symptoms were completely abolished during the period of hormone administration and for at least a week after its withdrawal The fasting blood sugar level rose from less than 10 mg per cent to 43 mg per cent in twenty four hours and to 90 mg per cent after the second day of treatment and remained at normal levels for the remaining two days *In the subsequent week without further therapy* the blood sugar tended to remain at levels intermediate between the hypoglycemic values of the pre treatment period and the normal values of the ACTH period Thereafter ACTH was administered in 18 mg doses every two days for ninety four days The fasting blood sugar values at the end of each forty eight-hour period when they would presumably be lowest ranged between 40 and 68 mg per cent The diet was unrestricted the infant gained weight and learned to walk No hypoglycemic episodes were observed during this time

During the period of ACTH administration the glucose tolerance curve became essentially normal the sharp fall and abnormally prolonged low level

characteristic of the pre treatment period being abolished No glycosuria was observed at any time Insulin hypersensitivity was reduced to a large extent by ACTH In contrast to the negative nitrogen balance induced by ACTH in normal adults the child maintained a positive balance as long as a full diet was taken

The four and one-half year old brother of this infant had a similar disturbance with severe hypoglycemia of three years duration Two successive operations had been performed with an even greater proportion of normal pancreatic tissue being resected to no avail As in his younger brother s case ACTH administration completely abolished the hypoglycemia Similar improvement was obtained from ACTH therapy in 3 other children with less severe recurrent hypoglycemia

Comment —Since the eosinophil response to epinephrine[70] in these patients was normal a deficiency in the capacity of the adenohypophysis to produce ACTH cannot be inferred A comparison of the glycogen content of liver biopsies before and after ACTH treatment by other investigators[71] revealed an increase in liver glycogen following the hormone administration By a study of the intravenous glucose tolerance test in combination with the fall in serum inorganic phosphorus Forsham[2] corroborated the finding that continued ACTH administration in normal individuals increases liver glycogen This may explain the tendency for children to outgrow the condition of idiopathic hypoglycemia as they acquire the glycogen stability of the liver of older children and adults Of incidental but extreme interest is the fact that following subtotal pancreatectomy in 2 children ACTH administration did *not* induce diabetes mellitus

b **Autonomic Nervous System Imbalance** —The terms nervous hypoglycemia hypoglycemic fatigue and autonomic nervous system instability are applied to a group of patients with vague symptomatology referable to the gastrointestinal cardiovascular and central nervous systems, who respond with a classical flat curve ' to either the oral or intravenous glucose tolerance test The best description of these individuals is Rynearson s candid generalization that they are low in a great many ways—not only is their blood sugar low but their blood pressure is low their blood count is low and the kidneys hang low They have a dropped colon or a dropped stomach—a good many of them have flat breasts A rounded glucose tolerance curve goes with well rounded breasts! [73] Karlan and Cohn[4] after a careful study of hypoglycemic fatigue in soldiers confess that the diagnostic criteria can be demonstrated in only a small percentage of patients with fatigue They find that when hypoglycemia occurs in an unstable person it may aggravate the instability They could offer no theory or explanation for this syndrome

These patients complain of fatigue and weakness especially on awakening This is relieved by breakfast reappears in the late afternoon and disappears after a large dinner There is associated morning headache vertigo, hunger, pyrosis pain in the chest dyspnea *etc* Exercise invariably aggravates the symptoms, in contrast to functional hypoglycemia where it often has no effect

There is little or no rise in the blood sugar level after glucose orally or intravenously[5] and consequently no significant response by a fall in the

level The blood sugar values maintain a fairly steady level between 60 to 90 mg per cent.

The treatment advocated by Portis[76] consists in diet, atropine phenobarbital and psychotherapy He proposes a diet high in protein moderately high in fat and relatively high in carbohydrate Frequent feedings are prescribed and free sugar in any form is forbidden This program contrasts with the simple and precise regimen originated by Conn[6] in the successful management of functional hypoglycemia Benzedrine sulfate (5 to 10 mg b i d) is often effective in relieving the fatigue and inertia

c **Functional Hypoglycemia** — The ingestion of glucose by normal individuals ordinarily produces a typical rise then a fall in blood sugar levels The terminal value at the customary third hour of the glucose tolerance test is usually below the fasting level—(Staub-Traugott effect) and may be accompanied by hypoglycemia symptoms This fairly common phenomenon was used very neatly by Thorn and his associates[77] in an investigation of the diet needed by the American worker for sustained performance and efficiency The typical high carbohydrate low protein and fat breakfast and lunch of the average worker led to mid morning and late afternoon hypoglycemic disturbances especially when the demand for increased industrial output during World War II interfered with supplementary nourishment during the working day The changes in blood sugar level caloric distribution and metabolic rate which followed the ingestion of an isocaloric breakfast composed of varying proportions of carbohydrate fat and protein were studied

Hypoglycemic symptoms were noted in many individuals three hours following the high carbohydrate meal coinciding with blood sugar levels around 70 mg per cent Differential derivation of the calories disclosed a rapid change from a predominantly carbohydrate metabolism to a predominantly fat metabolism between the second and third hour This change took place at the time when the hypoglycemic symptoms of hunger and weakness appeared These fluctuations did not occur following the isocaloric high protein and high fat meals In addition the high protein meal was followed by a sustained blood sugar level throughout the six-hour period of observation as Conn[6] had already demonstrated Other observers[109] deny the existence of such a physiologic hypoglycemic response to a high carbohydrate intake in *normal* individuals even after strenous exercise

Functional hypoglycemia represents an unusually sensitive responsiveness to the stimulus of a *normal* postprandial elevation in blood sugar In contrast post gastrectomy hypoglycemia represents an exaggerated response to an *abnormal* postprandial hyperglycemia

Diagnosis —Functional hypoglycemia accounted for at least 70 per cent of all cases of spontaneous hypoglycemia in Conn s series[6] The symptoms may include all the vasomotor motor and psychic manifestations of mild to moderate hypoglycemia described previously Mild vasomotor disturbances predominate except when the hypoglycemia serves as a trigger mechanism for the anginal syndrome carotid sinus syncope or cardiac arrhythmias[78]

The *diagnostic criteria* which distinguish functional hypoglycemia may be summarized as follows

1. *Attacks limited to the daytime, 2 to 4 hours after meals never during sleep*
2. *Normal fasting blood sugar levels*
3. *No intolerance to fasting or carbohydrate restriction*
4. *Typical glucose tolerance curve after standard dietary preparation*[8]
   a normal fasting level
   b normal or subnormal initial rise
   c rapid fall between 2 to 4 hours to low or subnormal levels
   d spontaneous return to normal levels by the fourth hour
5. *Excellent response to dietary management*
6. *Static nature of symptoms without progression in severity*
7. *Frequent association of emotional and autonomic instability with marked influence of emotional tension in precipitating attacks*

Although the *blood sugar response to epinephrine* is usually normal in contrast to organic hyperinsulinism where it often is diminished this test is too variable and nonspecific A significant difference is noted however, when compared to hepatogenic hypoglycemia where there is an extremely poor response

TABLE 32 — DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL AND HEPATOGENIC HYPOGLYCEMIA AND ORGANIC HYPERINSULINISM

	Functional Hypoglycemia	*Hepatogenic Hypoglycemia*	*Organic Hyperinsulinism*
Incidence	common	rare	rare
Relation of attacks to emotional tension	frequent	none	none
Pre-breakfast attacks	none	most frequent	most frequent
Daytime attacks	usual at 11 A M and 3 P M	infrequent	frequent
Effect of fasting or delayed meals	none	attacks precipitated	attacks precipitated
Progression in severity and frequency	none	always	always
Effect of exercise	variable	attacks precipitated	attacks precipitated
Fasting blood sugar level	normal	subnormal	subnormal
Glucose tolerance curve	1 normal fasting 2 normal curve 3 sharp fall to subnormal 2-4 hours 4 spontaneous return to normal	1 subnormal fasting 2 hyperglycemic plateau 3 gradual fall to subnormal 4-7 hours 4 no spontaneous return	1 subnormal fasting 2 low or diabetic curve 3 sharp fall to markedly low levels in 2-3 hours 4 no spontaneous return
Response to epinephrine	normal	poor	variable
Response to diet	excellent with *high protein-low carbohydrate*	1 good with *high carbohydrate* moderate protein 2 Worse with low carbohydrate	1 poor to fair with either high protein or high fat

The *insulin tolerance test* (5 units I V) is unreliable—the sole differential point between functional hypoglycemia and organic hyperinsulinism being a delayed blood sugar recovery in the latter which may be variable or immeasurable

The *fall in serum inorganic phosphorus* [2] combined with the glucose tolerance test cannot be used in differential diagnosis since it will be abnormal in all instances of depleted liver glycogen reserve

In summary the diagnosis of functional hypoglycemia should be made on the history of attacks in the postprandial period with constantly normal fasting blood sugar levels the tolerance to fasting or carbohydrate restriction the typical glucose tolerance curve after standard dietary preparation and the excellent therapeutic response to a high protein, low carbohydrate diet Adherence to strict interpretation of these criteria may prevent needless pancreatic surgery

Treatment —The fundamental basis of the management of functional hypoglycemia is aimed at preventing the initial rapid postprandial rise in blood sugar thereby reducing the secondary hypoglycemic response This was first attempted by means of frequent feedings of a high fat low carbohydrate diet [78] Then John [80] reported improvement with small doses of insulin (10 units) before each meal but this proved to be a burdensome method Since 1936 the *high protein low carbohydrate* diet suggested by Conn [6] has become the standard method of treatment The observations of Thorn and his coworkers [77] described above further strengthened the validity of this therapeutic approach The average diet contains 120 to 160 gm of protein 100 gm or less of carbohydrate and fat adequate to supply the remaining caloric needs This diet is given in 3 equal meals during the day Successful results are noted within two to three days after the diet has been instituted

The following report illustrates the typical course of functional hypoglycemia

Illustrative Case

An obese forty year old housewife complained of intermittent headaches blurring of vision tremulousness asthenia sweating and palpitation dating back to the last pregnancy fifteen years before There had never been any loss of consciousness or convulsions The symptoms appeared in the late morning and mid afternoon about three hours after a meal which usually contained an excessive amount of carbohydrate especially sweets Immediate relief was afforded by eating almost any kind of food but she preferred candy ever since a physician had informed her of her dangerously low blood sugar She seized upon this diagnosis as the excuse for her obesity

Apart from moderate generalized obesity physical examination proved negative and liver function studies and the basal metabolic rate were normal A single dose 100 gram oral glucose tolerance revealed the following curve

Hours	Fasting	½	1	2	3	4
Blood Sugar—mg per cent	93	185	170	92	60	85

At the third hour she complained of vertigo and headache

Following a twenty four hour fast a blood sugar level 111 mg per cent was obtained the patient having been free from hypoglycemic symptoms during this period

In view of the obesity a 1200 caloric diet containing protein 120 grams carbohydrate 75 grams and fat 50 grams divided into 3 equal meals effected complete relief from hypoglycemic symptoms and also permitted her to lose weight

Illustrative Case

A thirty five year old woman with essentially negative past and family histories reported the sudden onset two years before of convulsive seizures upon awakening in the morning. The seizures appeared about every one to two months except for a ten month period when he was symptom free. The attacks occurred only before breakfast, and were characterized by generalized convulsion, unconsciousness lasting ten minutes and biting of the tongue followed by nausea, vomiting, and asthenia. Recovery was spontaneous but slow and lassitude and asthenia persisted the entire day during which she ate little. Neither headache nor hunger had ever been noted.

Physical examination revealed no significant abnormalities and liver function studies and the basal metabolism were normal. Electroencephalography was performed synchronously with an oral glucose tolerance test, the values of the latter being indicated as follows

Hours	*Fasting*	½	*1*	*2*	*3*	*4*	*5*
Blood sugar—mg per cent	66	140	140	65	40	40	60

During the above five hours the EEG revealed a constant pattern of moderate bursts of 3 to 4 per second activity *not* varying with the changes in blood sugar level. There were no clinical or symptomatic manifestations of hypoglycemia *in the third or fourth hours of the glucose tolerance test. The pneu*moencephalogram was normal.

A diagnosis of idiopathic epilepsy with grand mal was made. The patient was discharged on dilantin and phenobarbital therapy without altering her usual dietary habits.

Comment —The abrupt onset of early morning convulsions in a thirty five year old woman warranted serious consideration of organic hyperinsulinism. Hepatogenic hypoglycemia and organic hyperinsulinism were excluded by virtue of the low but normal fasting blood sugar level and normal liver function studies. The relation of the seizures to fasting was not clear until the glucose tolerance test was performed during which true hypoglycemic values were obtained without concomitant alterations in the EEG or the development of clinical manifestations of either hypoglycemia or epilepsy. This is in keeping with the observation that epilepsy is neither induced nor aggravated by hypoglycemia.[68]

The subject of functional hypoglycemia can best be summarized by noting the geographic reason for the high incidence of the syndrome which led Harris[2] to recognize and organize the concept of hypoglycemia and hyperinsulinism. Most of the cases he reported we now recognize as examples of functional hypoglycemia provoked into clinical manifestations by the very prevalent Southern custom of drinking Coca Cola. Wilder[1] points out that consumed as it often is on an empty stomach the 27 gm of sugar in each bottle is tantamount to a glucose tolerance test.

8 **Increased Insulin Secretion—Organic Hyperinsulinism Due to Islet Cell Tumors** —Spontaneous hypoglycemia due to islet cell tumor of the pancreas presents a fascinating medical and surgical problem. The anatomic lesion, though physically small leads to most profound and potentially fatal reductions in the blood sugar level. Clinically the picture is limited to neurologic and psychiatric manifestations for the most part. Definitive diagnosis can usually be made without elaborate or expensive laboratory procedures. The dramatic cure by surgical excision is

often as not thwarted by the aggravating capacity of the tumor for concealment and inaccessibility within the pancreas and even ectopically

Incidence —*Functioning* tumors of the islet cells of the pancreas are rare Since Wilder's[3] first report in 1927 some 200 cases have been recorded At the Mayo Clinic 38 patients with spontaneous hypoglycemia on the basis of pancreatic islet cell tumors (verified at operation or necropsy) were observed over a twenty year period[51] We have seen 4 authenticated cases at the Mount Sinai Hospital in the past five years

The incidence is about equal in both sexes The average *age* of patients with benign adenomas is 41 3 years in contrast to that of 34 6 years in patients with metastasizing islet cell carcinomas[51] The malignant tumors being more active physiologically lead to earlier and more severe clinical manifestations The youngest patient with a benign adenoma was nine and one-half years old[13] the oldest sixty-eight years of age

Pathology —The term pancreatic islet cell tumor is often erroneously considered as being synonymous with hyperinsulinism Asymptomatic *non functioning* adenomas are frequently found on routine postmortem examination of the pancreas an incidence as high as 1 6 per cent having been noted[52] Six cases of *non functioning* islet cell carcinomas with metastases have been reported[51] 3 in patients with preexisting diabetes mellitus For the purpose of accuracy therefore pancreatic islet cell tumors should be qualified by the terms functioning with spontaneous hypoglycemia or with hyperinsulinism when they produce clinical manifestations

In a most complete study to date of 38 *functioning* islet cell tumors of the pancreas Lopez Kruger and Dockerty[51] noted the following incidence of pathologic findings

	per cent
1 Benign adenomas	70
2 Islet cell adenomatosis	2
3 Histologically malignant but non metastasizing islet cell tumors	20
4 Metastasizing islet cell carcinomas	8

Benign Adenomas —*Size* —Benign adenomas vary in *size* from 2 5 millimeters to 6 centimeters in diameter but *usually* are *between 1 and 2 centimeters* Rarely does an adenoma smaller than 5 millimeters produce clinical hyperinsulinism Therefore the report[53] of the postmortem discovery of a microscopic adenoma (no measurement of size recorded) in a six months old infant dying in hypoglycemia must be accepted with reservation The smallest adenomas in the Mayo clinic series were obtained from specimens which the surgeon had resected as suspicious tissue but which were overlooked by the pathologist as being negative for tumor Clinical relief of the symptoms promoted a careful review of the surgical material which resulted in demonstrating the tumors The size of the tumor has no relation to the severity of symptoms[54]

Location —Over one half of benign adenomas are located in the *tail* and at the *junction of the body and tail* of the pancreas paralleling the normal distribution of the islets of Langerhans The remainder are embedded within the *head* of the gland This is surgically significant since location other than in the body or tail of the gland may necessitate subtotal or total

pancreatectomy.[84] Finding and excising an adenoma does not relieve the surgeon from the responsibility of further exploration for additional tumors since Whipple[55] found multiple ones in 3 out of 27 cases. An adenoma of *accessory islet tissue* near the duodenum was found at necropsy in a patient in whom hyperinsulinism was unrelieved for eighteen years despite 3 partial pancreatic resections.[81]

Gross Pathology.—Adenomas may be pink or gray and contrast with the ivory-yellow appearance of the surrounding pancreas. Their cut surface is *smoothly homogeneous* unlike the normal lobulation of the gland. The *consistency* is usually *firmer* than that of the normal pancreas. *Encapsulation* has been considered an essential diagnostic mark of islet cell adenomas but Lopez-Kruger and Dockerty[81] failed to demonstrate this in almost half their cases although clear *delineation* of the tumors was evident. The tumor cells are arranged in the form of islands, cords and ribbons in both benign and malignant tumors.

Histology.—Hyalinization and fibrosis are correlated with long duration of symptoms. The cells appear *identical* with those of normal islets without appreciable difference in size. They are arranged in orderly fashion in a rich vascular framework. Cytologic staining for *beta granulation* is of no value in differentiating functioning from non-functioning adenomas, being often present in the latter and occasionally absent in adenomas with clinical hyperinsulinism.[81]

ADENOMATOSIS.—Multiple adenomas have been described in association with adenomas of the anterior pituitary,[49] thyroid[87] and parathyroid[81] glands. Frantz[85] suggests a multicentric origin for islet cell tumors with the *surgical implication* that the hyperplasia in the remaining pancreas may result in the return of hypoglycemic symptoms. One of her cases had a simple excision of a small adenoma near the tail of the pancreas with relief from hypoglycemic symptoms for but a few weeks. A second adenoma was removed two months later again with only temporary relief of symptoms. Partial pancreatectomy was finally performed after two months and multiple adenomas were apparent on gross examination of the specimen.

Nonspecific generalized hypertrophy and hyperplasia of the islets of the pancreas have been noted in a number of conditions[88] without associated hypoglycemia. Partial pancreatectomy was performed in a young girl suffering from hypoglycemia with convulsions and resulted in relief from the seizures with but mild elevation of the blood sugar level. Paradoxically the resected specimen revealed *hypoplasia* of the islet tissue.[88]

David and Campbell[8] in a review of the world literature on subtotal pancreatectomy for clinically undifferentiated hypoglycemia found only 5 instances of definite *islet hyperplasia* in the resected gland. However they noted 25 cases where perfectly *normal* pancreatic tissue had been resected with equal clinical improvement. Except where islet hyperplasia may represent the earliest stage of a rare adenomatosis, its causal relation to clinical hypoglycemia must be doubted.

HISTOLOGICALLY MALIGNANT BUT NONMETASTASIZING ISLET CELL TUMORS.—An amorphous group of *histologically malignant* but *clinically benign* functioning islet cell tumors was first described by Frantz[89] in Whipple's cases. These "borderline carcinomas"[81] are midway between

the simple benign adenomas and the frank metastasizing islet cell carcinomas in character. Like the carcinomas these tumors are large (2 centimeters or more), completely lack encapsulation and exhibit gross invasion of the surrounding pancreas usually and the blood vessels occasionally. Cellular anaplasia and the presence of mitotic figures intensify the resemblance further. Metastasis, however, has not been observed, although local recurrences have been reported. Frantz[88] dogmatically denies the malignant nature of these tumors, holding that "the suspicion of the pathologist, not the surgeon, has yet to be confirmed."

The clinical picture is equally "borderline," symptoms being more severe and more progressive than those in benign adenomas. The importance of the recognition of the characteristics of this tumor is illustrated in the following abstract of a case reported by Brunschwig.[90]

Illustrative Case

The patient, a young man, had presented an acute history of severe hypoglycemia with coma and convulsion, the picture of severe organic hyperinsulinism of five months duration. At exploration two pancreatic tumors were found, 1.5 and 6 centimeters in diameter respectively. Because frozen section examination of specimens from the tumors was reported as "*adenocarcinoma* Grade III," the *abdomen was closed* without an attempt at extirpation. Four months later, because the hypoglycemic attacks were *not increasing* in severity, Brunschwig suggested that the neoplasm *might not* have *metastasized*. Reexploration confirming the gross absence of metastases, a large tumor (15 centimeters in diameter) and part of the pancreas were resected, leaving the head and part of the neck of the gland.

Unusually severe postoperative diabetes mellitus without ketosis was an unexpected complication, a blood sugar value of 560 mg. per cent being obtained twenty-four hours after operation. Seventy to 100 units of insulin were *required for eleven days*, *gradually being reduced to 20 units for another eleven days* when normal blood sugar values were reached. Upon the patient's discharge from the hospital the glucose tolerance curve was normal. The patient thereafter was free from attacks and remained in good health.

Comment.—The sudden onset of severe hypoglycemic symptoms and the relatively short duration of the history at the time when medical aid is sought is typical of this functional malignant tumor. The conclusion drawn from the histologic picture of the specimens removed from the tumors reflects the general disagreement between pathologist and surgeon as to *the basis for interpretation of frank malignancy in these instances*. The subsequent clinical course substantiates the dictum of Frantz.[89] A unique feature was the large size of the tumor, roughly 15 centimeters in diameter, an extreme for solitary functioning islet cell tumors. This plus the adhesions induced by the first exploration made partial, almost subtotal resection of the pancreas necessary. An intriguing feature was the severe, though transient, diabetes mellitus which developed immediately after operation. An analogous reaction is seen in patients with Cushing's syndrome due to adrenal cortical tumors who develop postoperative shock because of contralateral adrenal atrophy.[91] In Brunschwig's patient the excessive insulin secretion by the tumor probably induced a relative functional insufficiency of the islets of Langerhans in the remaining pancreas. The sudden removal of the tumor plus a large amount of the pancreas (particu-

larly the islet rich body and tail) left a remnant of pancreatic tissue with insufficient capacity or reserve to carry on normal carbohydrate metabolism This insulin deficiency was only functional as indicated by the subsequent recovery three weeks later

METASTASIZING ISLET CELL CARCINOMA WITH HYPERINSULINISM — This, the pathologic lesion of the first case of proven hyperinsulinism [2] is fortunately rare Only 16 further cases with this tumor had been reported by 1947 [81]

The average age of patients with this tumor is 34 6 years *younger* than those with any other type of islet cell tumor The increased cytologic activity is reflected physiologically in the *earlier* appearance of symptoms and their rapidly *increasing* severity, the lowest blood sugar values for patients with spontaneous hypoglycemia being reported in this group One patient[81] was eighteen years of age and interestingly 2 patients gave a history of preceding diabetes mellitus

The tumors are *diffuse* involving the entire pancreas very *large* and lack encapsulation Necrosis and hemorrhage may be seen grossly *Hepatic metastasis* is always present but jaundice is notable by its absence

Histologically the pattern observed in benign adenomas prevails with the additional features of increased mitoses abnormal mitoses invasion of vascular and lymphatic channels and areas of necrosis and hemorrhage

None of the patients survived more than five years after onset of symptoms the average life expectancy being about one year

Almost unique in clinical medicine is the *gain in weight* which characterizes this type of carcinoma The abnormally increased caloric intake needed to ward off hypoglycemic attacks produces a deceptive *obesity* which masks the gravity of the underlying condition [81]

This type of carcinoma is further unusual in that *physiologic function* of the islet cells continues with the secretion of insulin *despite* the *cellular dedifferentiation* and anaplasia The following abstract of a case reported by Lopez Kruger and Dockerty [81] illustrates the characteristic features of this tumor

Illustrative Case

A forty two year old man in previous good health noted the onset of severe lower abdominal pain two months before death ensued Unrecognized hypoglycemic symptoms developed one month after the onset of pain and were characterized by muscular contractions episodes of rigidity opisthotonus paralysis of the facial muscles and right arm and progressive confusion and delirium Stupor with restlessness nuchal rigidity a right hemiparesis and fever all suggested the diagnosis of meningitis The spinal fluid showed a sugar content of 20 mg per cent while the blood sugar (after the administration of carbohydrate) was 69 mg per cent The patient succumbed in coma within forty-eight hours

Necropsy revealed carcinoma of the tail of the pancreas with involvement of the peripancreatic nodes liver left kidney and the spinal cord Histologically the tumor displayed marked similarity in form and architecture to normal islet tissue despite marked cellular atypia numerous mitoses and invasion of capillaries and veins by groups of tumor cells Beta granulation was demonstrable in some cells both in the original tumor and in the metastatic deposits

Comment —The relatively young age of the patient, the rapid onset and fulminating clinical course plus the severe central nervous system involve-

ment secondary to hypoglycemia indicate the highly malignant nature of this tumor. The *increased cytologic activity* with *increased physiologic function* yields a clinical picture of hypoglycemia which develops earlier, progresses more rapidly and produces more severe neurologic damage than that found in clinically benign adenomas.

No curative or palliative treatment is available at present. The extreme invasiveness of the tumor with rapid metastasis precludes surgical success by the time the patient has been operated upon. *Alloxan*, first tried by Brunschwig and his associates[97] in 1943, has failed to influence the relentless progress of the disease.[98, 99] Neither normal nor cancerous islet tissue is affected by alloxan administration in these patients. Sprague[99] found severe and fatal damage to the liver as a result of alloxan therapy, while the islet cells of the tumor and the uninvolved pancreas were "virtually untouched."

Insulin Content of Tumors.—The insulin content of the normal pancreas averages 1.7 units per gram of gland.[33] Assay of islet cell tumors yields an increased insulin content ranging from 3 to 100 units per gram of neoplastic tissue.[94] This, however, bears no relation to the severity of the clinical picture, the degree of hypoglycemia, or the type of tumor, whether it be benign or malignant. The release of insulin from these tumors may be erratic and irregular in the opinion of Whipple[55] and others.[95] Conn,[96] on the other hand, insists that insulin secretion is excessive at all times, not only in the fasting state. No explanation is available for the fact that the entire insulin content of a tumor is less than that of the whole normal pancreas. Metastatic deposits of malignant islet cell tumors yield an increased insulin content equal to that of the parent neoplasm.

An intriguing plan to use the excessive insulin secretion of islet cell tumors in the treatment of patients with severe diabetes mellitus led Whipple[56] to transplant tissue cultures of neoplastic cells into these patients. Unfortunately the four cases so treated displayed neither a decreased insulin requirement nor any evidence of growth of the transplant.

Clinical Manifestations of Islet Cell Adenoma.—The vasomotor, motor and psychic manifestations of hypoglycemia already described in the introduction to this chapter characterize the clinical history of patients with benign functioning islet cell tumors. Certain additional features besides the classical history are specific for this group. These include *chronicity* with *progression in severity* of symptoms, eventually fatal outcome if untreated, evidences of associated *central nervous system damage* which becomes less reversible in the course of time, *failure to respond to dietary management* and *dramatic cure upon removal of the tumor*.

The history suggests the diagnosis because of the time relation of hypoglycemic attacks to meals. Symptoms occur typically *during sleep* or *on arising* before breakfast. They are precipitated during the day by eating inadequately, delay in or omission of a meal and strenuous physical effort. Spontaneous recovery from hypoglycemia is slow and more difficult with progression of the condition. The response to food, especially carbohydrate, is dramatic, as is the recovery after intravenously administered glucose in profound hypoglycemia.

The progression of symptoms from moderate to severe manifestations reflects the *duration* of hypoglycemia rather than its intensity. Fraser and his associates[16] performed the most detailed study of the clinical picture of benign adenoma in a patient subsequently cured by excision of the tumor. They observed no symptoms when the blood sugar level was above 70 mg per cent. At levels between 60 to 45 mg per cent asthenia, lethargy, dreaminess and depersonalization appeared. The latter was characterized by increasing difficulty of expression and thought, aimless actions, negativism and other behavioristic abnormalities. During this stage physical examination was negative with dry skin and unaltered pulse and blood pressure.

After the blood sugar had continued at a level of 45 mg per cent for about a half hour drowsiness and coma set in. At this point obvious physical signs were manifest: the skin became flushed and moist, the blood pressure decreased, and the pulse rate increased. Without further decline in the blood sugar level complete unresponsive coma appeared about forty five minutes after the onset of drowsiness. Now all deep reflexes were lost along with the response to painful stimuli. Sweating was profuse and the respiration became shallow.

Except for variation in the vasomotor symptoms all the attacks adhered to this pattern. These variations were observed to be related to the rapidity of onset of hypoglycemia. Flushing, sweating and restlessness were noted when the attacks came on slowly in contrast to the more precipitous episodes when these symptoms failed to appear until deep coma supervened.

Although symptoms appeared only when the blood sugar level fell to below 50 mg per cent, their intensity could not be correlated with variations within the subnormal range. Thus, as mentioned, deep coma was observed with values maintained at 45 mg per cent, while on occasion only first stage symptoms were manifested with lower levels such as 28 mg per cent.

The response to glucose also reflects the *duration* rather than the depth of hypoglycemia. The decreased cerebral oxygen utilization associated with hypoglycemia[18] leads to central nervous system damage which may be irreversible if sufficiently prolonged. A case of islet cell adenoma had been in deep coma for one and a half days when restoration of the blood sugar level was effected without influencing the clinical course and death followed sixteen days of unconsciousness.[100] Similar instances have been reported by others.[7, 8, 9] In general, both the amount of glucose and the length of time of its administration necessary for recovery will increase with the duration of hypoglycemia.

Attacks of hypoglycemia are often more frequent during *menses*.[16] *Pregnancy*, however, has been observed to cause amelioration of symptoms of islet cell adenoma.[9, 101] A young woman presented a history of complete cessation of hypoglycemic symptoms during pregnancy with recurrence thirteen days postpartum.[101] In the fifth month of a succeeding pregnancy the same phenomenon was noted with disappearance of symptoms to the point where consumption of sugar was no longer necessary. Nine days post-

partum the most severe attack ever experienced by the patient occurred with unconsciousness lasting twelve hours (blood sugar level 20 mg per cent) Two months later exploration revealed a typical adenoma of the islet cells in the head of the pancreas Its resection afforded complete clinical recovery It is not known whether the remission during pregnancy was related to the usual increase in the glycogenic corticosteroids during this period

The typical history and course of organic hyperinsulinism due to a benign islet cell adenoma is illustrated in the following case whom we had observed This has been reported previously by Bernstein[10]

Illustrative Case

A twenty nine year old woman a pianist by profession had been in good health until July 29 1943 when she retired at 11 P M and continued to sleep until 4 30 the following afternoon despite all efforts to awaken her When finally aroused she was bewildered and disoriented perspiring profusely Her speech was thick and she complained of vertigo and diplopia After eating breakfast recovery was prompt For the next three weeks however there was persistent drowsiness and she could rarely be awakened before 1 P M There were no convulsive seizures Although conscious of the overpowering nature of the lethargy she found it impossible to arouse herself Similar episodes would occur when a meal was inadvertently skipped She soon learned the efficacy of sweetened drinks in preventing and controlling her symptoms and if awakened during the night to drink orange juice fortified with sugar the morning attacks would be averted

Her own description of her symptoms follows For several successive days I would be in a semiconscious state before arising During these periods which would last for ten minutes to as much as five hours I was told that I answered questions and would even eat breakfast without the slightest knowledge of having done so At other times I was told that every possible attempt to awaken me would be futile particularly if I clenched my teeth and refused food the attacks would then last much longer Shortly after eating I would become vaguely aware of my surroundings and on fully awakening would demand to know the date and hour Early in my illness I would frequently awaken at night in a profound daze and find myself incapable of consecutive thought I also found it impossible to organize my daily routine I would fall asleep while reading letters my fingers would fail to find the piano keys and I was unable to concentrate on reading During the latter part of the day although I never lost consciousness I had frequent sensations of vagueness lightness unreality and total exhaustion sometimes associated with drenching perspiration which were relieved as soon as I took sweet or fatty foods relief would then last for an hour or two when the haze would return I was fully aware of my growing apathy dullness and stupidity Even when I was placed on a high fat diet with frequent meals these sensations though milder and more transient did not entirely disappear

The clinical picture was at first interpreted as a profound psychasthenia which had been precipitated by separation from her parents hard work and the prolonged intense heat of the city where she resided She had been emotionally unstable introspective and easily frightened since early childhood Trivial annoyances would loom large and fresh situations precipitated intense anxiety

She was admitted to a hospital in another city on August 23 1943 Physical examination there was negative in every detail On the regular hospital diet and bed rest she had no discomfort until August 27th at 9 A M when she was found to be semicomatose and perspiring profusely She was aroused with difficulty and resisted examination Her responses were sluggish and inaccu

rate Speech was slurred her expression stupid and she was unable to focus adequately Her gait was staggering The blood sugar level during the attack fell to 37 mg per cent On the following morning she had a similar episode with inability to speak, expressionless facies and involuntary movements of the right angle of the mouth A "fasting test" was performed on August 30th and when breakfast was withheld until 9 A M she suddenly became dazed, was drenched in perspiration and unable to speak Within two minutes after the intravenous administration of 40 cc of 50 per cent glucose she was fully alert, inquired the cause of the commotion and fell to eating her breakfast voraciously On September 3rd she was found deeply comatose at 9 A M, there was marked twitching of the left corner of the mouth The blood sugar level was found to be 10 mg per cent Response to intravenous dextrose was almost immediate On the next day she automatically drank orange juice while in a semi stupor with prompt response and no memory of the episode

Laboratory Investigations —Fasting blood sugar levels were successively 37 28 43, 36 and 45 mg per cent A glucose tolerance test with a fasting figure of 28 mg showed after the ingestion of 100 gm of glucose hourly figures of 36 47 52 and 59 mg per cent thereafter

A high fat and protein diet with frequent feedings *both day and night* was instituted and the major hypoglycemic episodes disappeared At follow up on November 30 1943 the blood sugar level was 86 mg per cent

Although the severe hypoglycemic episodes had been controlled by the high fat-frequent feeding regimen she complained of extreme fatigue, absent initiative aimlessness tremulousness inability to concentrate and an oppressive sensation which she described as a "veil" over her head The high fat diet had induced a degree of obesity which she felt was both cumbersome and unsightly and having to awaken for food during the night annoyed her She was admitted to The Mount Sinai Hospital on March 14 1944 Physical examination apart from obesity was negative

Course —She was given the regular hospital diet and on the day following admission was lethargic before breakfast but was perfectly well twenty minutes after eating The fasting blood sugar level was 50 mg per cent On March 17th breakfast was delayed because of a gastro intestinal roentgen series and she had a seizure characterized by weakness hunger and sweating On March 21st food was purposely withheld for eighteen hours and at 12.30 P M she became apprehensive irritable and complained of vertigo and diplopia Articulation was clear and orientation good After drinking orange juice with sugar her symptoms vanished On March 23rd she experienced a very severe hypoglycemic attack at 5 30 A M with profound lethargy during which the blood sugar reached the level of 10 mg per cent The episode was followed by retrograde amnesia

Laboratory Data —Fasting venous blood sugar figures were successively 50 42 50 30 10 and 34 mg per cent A glucose tolerance test revealed a fasting value of 50 mg per cent followed by levels of 100 200 240 240 mg per cent at hourly intervals respectively The patient had been eating a high fat diet for almost a year and this was considered sufficient cause for the "diabetic" curve Tests of liver function were normal The gall bladder however did not visualize adequately

It was felt that the recurrent episodes of hypoglycemia with blood sugar levels of 10 to 50 mg per cent appearing with some regularity from twelve to eighteen hours following the ingestion of food indicated the presence of an islet cell adenoma with hyperinsulinism

Operation —On March 29 1944 a laparotomy was performed under cyclopropane anesthesia after pre-operative preparation with 5 per cent intravenous glucose Through an upper abdominal transverse incision the lesser sac was entered by cutting through the gastrocolic ligament A careful exploration was made of the body and *tail of the pancreas but no adenoma was found* This required mobilization of the organ from below upward Most of the head of the pancreas was explored without result With dissection of the second portion of the duodenum forward and to the left it was possible to palpate

the whole head between two fingers After considerable dissection an adenoma was finally located in the uncinate process between the superior mesenteric vessels The tumor was soft reddish purple and measured 1.5 cm in diameter It was dissected free from the pancreatic tissue and removed Inasmuch as no other tumors were demonstrated the wound was closed

Histologic study of the removed specimen disclosed an adenoma of the islands of Langerhans with hyalin changes There was an immediate post-operative hyperglycemia of 300 mg per cent with fasting levels of 170 to 140 mg per cent the next two days Insulin was not given Thereafter fasting blood sugar levels varied from 75 to 100 mg per cent until her discharge from the Hospital A sugar tolerance test on April 24th disclosed a fasting blood sugar level of 75 *mg and 90 105 115 and 105 mg per cent at one two three four and five* hours respectively On May 2nd the fasting blood sugar level was 80 with 125 135 90 and 95 mg per cent at thirty minutes one hour two hours and three hours thereafter An electroencephalogram on April 25th disclosed a normal record She was discharged on May 15 1944 with an unrestricted diet and completely relieved of the hypoglycemic attacks When last seen she was alert energetic and entirely free of any discomfort identified with her former illness

Comment —The sudden onset of gross hypoglycemic symptoms followed oversleeping and an unusual delay in breakfast However the patient's preexisting anxiety symptoms probably masked milder episodes which were overlooked The criteria for a definitive diagnosis of an islet cell tumor were contained in the subnormal fasting blood sugar level (37 mg per cent on admission) the response to glucose orally and parenterally, and the typical symptom pattern appearing on fasting

The first flat hypoglycemic glucose tolerance curve followed a period *of a spontaneously chosen high carbohydrate diet and contrasts with that* seven months later when a high fat regimen yielded an abnormal sustained rise from a subnormal level This may be related to Conn's[96] observation that the antecedent diet determines the shape of the glucose tolerance curve in organic hyperinsulinism as well as in the normal state

The relief obtained from the high fat high protein diet with feeding every two hours proved of benefit in preventing the symptoms of severe hypoglycemia only Milder hypoglycemia persisted and the nuisance to the patient of eating around the clock was exceeded only by the disfiguring obesity

Exploration proved difficult because of the patients obesity and the location of the tumor The long duration of the condition was indicated histologically by the hyaline changes in the adenoma A mild transient postoperative hyperglycemia frequently seen in these patients resolved completely

Diagnosis —The diagnosis of islet cell tumor is made principally on the basis of the history and fasting blood sugar values

RELIABLE DIAGNOSTIC CRITERIA

1 History of attacks with definite symptoms pattern coming on during fasting state 2 Fasting blood sugar levels of 50 mg per cent or less 3 Immediate recovery upon the administration of glucose	Whipple's[5] triad for organic hyperinsulinism

4 History of previous good health } Wilder's[15] addition to
5 Intolerance to fasting } the triad
6 Glucose tolerance curve after standard dietary preparation—Conn[6]

Whipple's third point is extremely important in the clinical differentiation of hypoglycemia from syncope and unconsciousness due to other causes. Although in case of prolonged hypoglycemia the response to energetic glucose administration may be undramatic.

Wilder's additional criteria were designed to exclude cases of autonomic imbalance and functional hypoglycemia. The *fast test*[15] consists in withholding food for a period of thirty hours during which time blood sugar determinations are made every six hours. Water and mild physical activity are permitted. When symptoms appear they are allowed to progress to the point of disorientation when glucose is administered. This should coincide with a blood sugar determination of 40 mg per cent or less.[15] Naturally the appearance either of symptoms or of a subnormal blood sugar value calls for termination of the procedure. It is contraindicated as a diagnostic measure in hepatogenic hypoglycemia or endocrine insufficiency.

The *glucose tolerance test* as an aid in the diagnosis of organic hyperinsulinism has been the subject of much controversy. Wilder[15], Whipple[85] and others[94] claim it to be of no value other than as a test of liver function, placing more reliance upon the fasting blood sugar determination. It must be pointed out that except for the low fasting blood sugar level the glucose tolerance curve may be diabetic in character in fully half the instances. The factors responsible for this type of glucose tolerance curve are not definitely established. It is possible that they may be related to the nature of the diet, the depletion of liver glycogen and to other as yet unidentified influences. In addition the character of the curve may vary from time to time in any given patient. Conn[96] on the other hand claims that only with standard dietary preparation can a valid interpretation of the curve be made. Using his criteria very sharp differentiation may be obtained between organic hyperinsulinism and hypoglycemia on functional and hepatogenic bases. *Prolongation* of the glucose tolerance test beyond the third hour to five or six hours provides even more significant data than can be obtained from the shape of the curve. In organic hyperinsulinism the blood sugar level continues to fall after the third hour to progressively hypoglycemic values without any tendency to spontaneous return towards the fasting point. In effect this is a combined result of the exaggerated response to ingested glucose coupled with an abortive fasting test.

The *insulin tolerance test* devised by Fraser[16] requires four days of preparation with a high carbohydrate diet beforehand. Insulin is given intravenously in a dose of 3.7 units per square meter of body surface. The blood sugar levels are determined at twenty minute intervals for a period of two hours. Normally the maximum fall to about 50 per cent of the fasting level occurs within twenty to thirty minutes after injection. At the end of the second hour the blood sugar level should return to within 10 per cent of the fasting value. This is delayed in cases of organic hyperinsulinism and never approaches the normal response during this time.

Although popular abroad this procedure has never gained widespread

acceptance in this country. Wilder [14] and Whipple [88] this time in agreement with Conn[4] dismiss the test as variable and unnecessary for the diagnosis. The same unreliability is voiced[4] with regard to the *fall of the blood sugar level in response to epinephrine* which is an index of liver glycogen reserve.

The demonstration of *electroencephalographic changes during hypoglycemia*[15] is nonspecific and of no clinical diagnostic value. The appearance of an epileptic pattern on EEG during hypoglycemia is promptly abolished with the return of the blood sugar level to normal. Persistence of abnormal waves *at this time suggests an etiology other than hypoglycemia* except in cases of severe brain damage due to the latter.

The following abstract of a case observed at our hospital has been reported previously by Wechsler and Garlock.[104]

Illustrative Case

A twenty-eight year old woman was admitted to the hospital on December 1, 1942 with a history of previous good health until the morning of September 15, 1942. She awoke with difficulty, appeared lethargic, asthenic and presented a vacant stare. Recovery followed the ingestion of food. Retrograde amnesia for this and future episodes was noted. One month later, twenty-*four hours after the religious observance of a fast day, a similar episode occurred.* After a free interval of one month the morning attacks became more frequent and were associated with frantic irrational behavior.

Physical examination except for moderate obesity was negative.

The fasting blood sugar levels ranged between 20 to 45 mg. per cent. During a hypoglycemic episode an EEG revealed a large amount of 4 to 6 per second delta activity which disappeared promptly with the administration of 15 grams *of glucose intravenously.*

Exploratory operation revealed an easily resectable adenoma in the tail of the pancreas. This proved to be an islet cell tumor on histologic examination. Complete recovery followed extirpation and the electroencephalographic pattern reverted to normal.

A measurement of increased insulin secretion or excretion would be desirable for the specific diagnosis of functioning islet cell tumors. The minute amounts of *insulin excreted* in the *urine* require concentration of extremely large volumes of urine in order to obtain sufficient material for bio-assay. Mirsky[70] overcomes this difficulty by *removing the urinary* salts by dialysis followed by shell freezing and dessication by the lyophile process. *This method* permits concentration of an entire twenty-four hour urine collection down to small amounts of dry powder. The accumulation of several days urinary excretion in such small volume is then extracted for insulin and the latter assayed biologically. The average daily urinary excretion of insulin in normal subjects is 0.16 units. Only minute amounts of exogenously administered insulin can be recovered in normal individuals indicating its rapid destruction.

The possibility that excessive *endogenous insulin secretion might escape* this destructive process seemed to suggest that such an assay in organic hyperinsulinism might yield abnormally high recoveries from the urine. We observed the following patient with this procedure in mind. The case was reported by Wilner and Weinstein.[13]

Illustrative Case

A forty nine year old woman was admitted to the hospital on April 15 1947 with a four year history of syncope before breakfast, associated with restlessness confusion, bladder incontinence and partial amnesia At first the attacks occurred infrequently and in the early morning only Then they appeared in the late afternoon as well always relieved by food Numbness of both hands and feet developed after several months

A diagnosis of hypoglycemia made by the physican in 1942 was confirmed by blood sugar determination A high carbohydrate diet with frequent feedings reduced the severity and frequency of attacks for about two months when they returned as before

A glucose tolerance test in 1944 revealed the following

Hours	*Fasting*	½	*1*	*2*	*3*
Blood sugar mg per cent	60	60	65	50	60

All other tests for possible causes of hypoglycemia being negative, operation was advised but the patient refused

In 1946 the diet was changed to a high protein moderate carbohydrate and fat regimen which effected some improvement in symptoms Although the episodes recurred with increasing severity the diagnosis of islet cell tumor was *discarded* since the fasting blood sugar level did *not* fall below 50 mg per cent on many occasions Diagnoses of hypothalamic and hepatogenic hypoglycemia were entertained Brucellosis was considered an explanation of the symptoms and the vaccine was administered to no avail The neurologic symptoms progressed in severity and a paretic gait without ataxia appeared

Physical examination was not remarkable except for obesity and the neurologic findings All deep reflexes were absent Bilateral positive Babinski, Chaddock and Oppenheim signs were obtained Position and vibration sense in the toes were impaired There were no sensory disturbances or cranial nerve involvement The diagnosis of a posterior column disorder on the basis of hypoglycemia was made

The morning following admission to the hospital in 1947 provided the medical staff with a picture of severe hypoglycemia with disorientation and agitation finally terminating in unresponsive coma During this time the blood sugar was determined as being 10 mg per cent Response to intravenous glucose was dramatic as usual

The twenty four hour urine collection obtained the day before operation was sent to Dr I A Mirsky for insulin assay

Exploratory operation was performed on May 27 1947 Careful examination of the pancreas failed to reveal any abnormality Therefore partial pancreatectomy was performed with removal of the tail and most of the body of the gland Examination of the resected pancreas revealed an adenoma 1 centimeter in diameter embedded in the tail

Prompt recovery followed except for a mild hyperglycemic glucose tolerance curve one week postoperatively Subsequently this became normal The neurologic signs and symptoms have persisted unchanged to date

Urinary excretion of insulin as determined by Mirsky revealed an increased preoperative value of 1 56 units daily excretion compared with the average normal daily excretion of 0 16 units per day Another determination obtained two weeks after operation was reported normal 0 16 units

Comments —This case presents several extremely instructive points

1 The marked *increase* in daily *urinary excretion of insulin* just prior to operation and the normal value obtained two weeks later *cannot* be accepted as specifically indicating excessive secretion of the adenoma Establishment of the validity of the procedure awaits its application in similar instances The influence of the antecedent high carbohydrate feed-

ings and the preoperative glucose administration in stimulating increased insulin secretion from the *normal* islet tissue[64] must be taken into consideration in interpreting the findings The practical value of the test has yet to be demonstrated

2 The clinical history of typical hypoglycemic attacks should have been sufficient for the diagnosis Yet *failure to obtain a fasting blood sugar level of 50 mg per cent* or below deterred one of the most experienced surgeons in this field from urging exploration This led to a delay of two years during which time the neurologic damage advanced to serious disabling proportions The patient was subjected to innumerable varying diagnoses and therapeutic procedures except the correct one Finally as *the episodes increased in severity and frequency the underlying condition* was apparent to all It would seem that in the early stages of islet cell adenoma the rigid application of Whipple s criteria may deprive the patient of timely cure Whipple [64] by the strict application of his triad found islet cell tumors in 35 of 41 patients

3 Since blind resection of the tail of the pancreas will remove 50 per cent of islet cell adenomas and resection of the body in addition to the tail will account for 20 per cent more [81] surgical judgment called for partial pancreatectomy when exploration failed to reveal the adenoma The tumor in this case was embedded so completely as to elude discovery by palpation

4 The *neurologic complication* of combined postero-lateral column disease of the spinal cord must be considered secondary to recurrent and protracted hypoglycemia Campbell and his associates[80] noted generalized neurologic residua in their third case of islet cell tumor In addition to mental confusion incontinence and speech disturbances muscle wasting and incoordination occurred with incomplete recovery over a period of years Peripheral neuropathy with foot drop and atrophy of the muscles of the hand and calves have been reported recently both here[12] and abroad[11] in patients with proven islet cell tumors Both reports indicate that an untreated period of intermittent hypoglycemia lasting about two years may be sufficient to produce this type of nerve damage

A patient who had received x ray treatment to the pituitary for acro megaly associated with hyperglycemia developed severe hypoglycemic symptoms two years later [49] The diagnosis of islet cell tumor of the pancreas was arrived at after primary consideration of hypoglycemia due to adenohypophyseal insufficiency had been excluded At operation 2 adenomas were found and removed successfully with clinical recovery

Treatment of Benign Adenomas —EMERGENCY TREATMENT —1 *Intra venous glucose* administration is the only effective measure in the treatment of severe hypoglycemia

2 Glucose orally *in the form of sugar* juices and sweet drinks is adequate in relieving the less severe forms when the patient can be made to swallow

3 Epinephrine *0 5 cc subcutaneously* is usually of benefit in mild hypoglycemia It is ineffective in the severe hypoglycemic state

PALLIATIVE TREATMENT —All measures other than *operative removal* of the tumor are ineffective for complete and permanent relief of symptoms

They may ameliorate the severity of the condition but should be used only temporarily until operation is performed

1 *Frequent feeding* around the clock night and day every two hours will prevent the development of symptoms at the cost of increasing obesity and great annoyance to the patient

2 *High protein (120 to 150 gm) low carbohydrate (75 to 100 gm) diet* with a night feeding on retiring is useful in the early stages when symptoms are mild but fails as the condition progresses

3 *Epinephrine in oil* 1 cc intramuscularly twice daily is occasionally successful in preventing symptoms during the intervals between meals

4 *Anticonvulsants—(e g* Dilantin Sodium) are often effective in abolishing the violent convulsive component of severe hypoglycemia when administered prophylactically in doses of 0 1 gm t i d

The following have proven ineffective in the clinical management of organic hyperinsulinism

1 *Adrenal cortical extract*—whole and lipo adrenal[96] extract
2 *Anterior pituitary extract*—crude and growth fractions,[59] and ACTH
3 *Alloxan*[63]
4 *Ephedrine*[96] and *amphetamine*[16]

Conn[59] found that administration of the same extract of anterior pituitary gland which is diabetogenic in the dog rapidly intensifies the hypoglycemia of patients with pancreatic islet cell tumors He found the daily intramuscular administration of 30 cc of adrenal cortical extract totally ineffective in raising the blood sugar level or in preventing attacks[6] Recently we employed ACTH for the treatment of a patient with hyperinsulinism Although he did exhibit less frequent episodes of hypoglycemia conclusive objective evidence of improvement was lacking

The failure of alloxan therapy in the treatment of malignant metastasizing islet cell tumors has been described above The same resistance to the cytotoxic effect of the drug is displayed by the cells in benign adenomas Conn and Hinerman[59] noted a decrease in carbohydrate tolerance after nine days of alloxan administration (60 gm total) to a patient subsequently operated upon for a benign islet cell tumor This effect was indicated only in the glucose tolerance curve (due possibly to liver damage) no relief being obtained however from the severe morning hypoglycemic attacks Pathologic examination of the adenoma and the resected portion of normal pancreas revealed changes in the normal islets only the tumor cells remaining intact They concluded that the amount of alloxan needed to produce destruction of islet cell tumors would most likely be lethal to the patient Sprague[99] reported one such instance of lethal damage to the liver from alloxan

Deep x ray treatment directed at the pancreas has been reported as effecting partial relief from hypoglycemia in a patient previously subjected to subtotal pancreatectomy followed by a large amount of alloxan (168 grams[6])[106] This patient also received 2695 cc of crude anterior pituitary extract (prepared by Young) without benefit Partial pancreatectomy had been performed 3 times removing the body the tail and finally the head of the gland successively Very little pancreatic tissue was left over yet severe hypoglycemia persisted It is remarkable that despite the violent

attacks against the pancreas by every avenue of approach hypoglycemia has persisted to date although in less severe form than before. David and Campbell[52] reported a similar failure of alloxan therapy after subtotal pancreatectomy.

SURGERY.—Simple excision of a demonstrable adenoma effects a dramatic and complete cure. In the absence of such good fortune subtotal or total pancreatectomy offer a fair chance for equally successful recovery.

Whipple has been able to find islet cell tumors at operation in 85 per cent of patients subjected to exploration,[49] undeniably the most successful series reported. The experience of the Mayo Clinic[53] indicates that the surgeon can expect to find a tumor in 50 to 60 per cent of cases on the first exploration. The presence of multiple tumors (10 to 20 per cent) will necessitate partial pancreatectomy or repeated exploration.

"Blind" resection of the tail of the pancreas will remove 50 per cent of the tumors. Resection of the body in addition to the tail will account for 20 per cent more. Therefore partial pancreatectomy offers an appreciable chance for a successful result. Total pancreatectomy[54] will be necessary for the small tumor buried in the head of the gland, the site of 20 to 30 per cent of the adenomas. Extra-pancreatic location is extremely rare.

An *analysis of the surgical experience* with 22 islet cell adenomas as derived from the published material of Lopez, Kruger and Dockerty is presented in the following:

- 12 were *easily recognized* and removed by simple excision.
- 10 were *not found*; of these
  - 3 were subjected to *partial pancreatectomy* with removal of the tail and body in the hope of finding the tumor in this location.
    - 1 instance the resected portion *contained* the *tumor*.
    - 2 were reoperated upon.
      - *Adenoma found this time* and excised in 1 patient.
      - *Part of head of the pancreas removed* in other patient, and a deeply *embedded* tumor was *found* to be included *in the specimen*.
  - 1 *death* with *negative exploration* yielded an *adenoma* in the *head* at *necropsy*.
  - 2 were subjected to total pancreatectomy with adenomas found deep in the head close to the duodenum.
  - 1 patient was subjected to 3 *partial resections* without discovery of the adenoma; symptoms persisted eighteen years until death. *Necropsy* revealed an *adenoma* of *accessory islet tissue* near the duodenum.
  - 2 patients were subjected to *resection* of "*suspicious tissue*" which was reported "*negative*"; yet relief of symptoms prompted review of the specimens with discovery of the smallest functioning adenomas on record (2.5 mm. and 4 mm. in diameter).
  - 1 patient was subjected to multiple resections for adenomatosis.

The above observations lead to the conclusion that "the surgeon performing an operation for the relief of hypoglycemia must be prepared to carry out procedures ranging all the way from simple excision of an easily identified and readily shelled out tumor to total pancreatectomy."[55]

The surgical challenge presented by pancreatic islet cell tumors is made more difficult technically because of the associated obesity. The methods

careful detail with which the possibility of an adenoma must be pursued is indicated by the following abstract of the operative procedure[105] in a patient whom we have observed for eight years

Operation — The abdomen was opened through a long upper transverse incision and the lesser sac exposed by incising the gastrocolic ligament The stomach and colon were then retracted bringing into view the entire body and tail of the pancreas Careful palpation of this portion of pancreas failed to reveal anything suggesting a tumor The peritoneum was incised along the inferior border of the pancreas and the organ was dissected upwards in order to expose its posterior surface The pancreas was finally suspended from the splenic vein and artery and still no tumor was found Once more the peritoneum was incised this time along the outer border of the second portion of the duodenum The duodenum, head and neck of the pancreas were displaced mesially, thus affording the operator an excellent opportunity to palpate this section of the organ Again there was nothing to suggest the presence of an adenoma The uncinate process was next exposed and found to be normal After considerable discussion with the attending medical staff it was decided to perform a subtotal pancreatectomy This was done by freeing the pancreas from the splenic vein and artery up to the neck at the point where the superior mesenteric vessels cross over the tip of the uncinate process The pancreas was ablated at the neck and the edges closed over with silk sutures

Pathological report — There were no significant changes in the microscopic appearance of the gland

The history and clinical findings satisfied all the diagnostic criteria for islet cell tumor Although the patient suffers intensely from hypoglycemic symptoms (never allowing himself to sleep more than two hours at a time without awakening for food) he refuses reexploration and total pancreatectomy

Partial pancreatectomy equal to massive resection yielded cures in 15 of 25 patients in whom no pathologic lesion could be demonstrated in the resected gland[92,104] The first total pancreatectomy for islet cell adenoma performed in 1942 had survived five and one half years at last report, being in apparent good health except for the surgically induced diabetes mellitus which was of only moderate severity

Preoperative care simply requires the administration of 5 to 10 per cent glucose intravenously carried on throughout the operation and as long as needed after it The development of postoperative hyperglycemia is fairly common but is so transient as to make insulin administration usually unnecessary Occasionally as in Brunschwig's[90] and Conn's[63] cases the manifestations of untreated severe diabetes mellitus make insulin therapy necessary for a few weeks at most.

9 **Factitious Hypoglycemia (Surreptitious Insulin Administration)** — Simulation of the clinical picture of islet cell tumor by factitious hypoglycemia may be so artful as to deceive an unsuspecting physician into proposing or performing a futile exploratory operation

Because of severe hypoglycemic attacks associated with episodes of unconsciousness, a graduate nurse was explored with negative operative and pathologic findings The capricious clinical course aroused the sus

picions of Conn[197] particularly when extremely *high respiratory quotients* were obtained in the fasting state. The sudden increase in the respiratory quotient suggested the surreptitious ingestion of carbohydrate or the administration of insulin in the absence of hyperventilation as the only other possible explanation. Careful search of the lavatory led to the discovery of a skillfully concealed vial of U-80 regular insulin. Without apprising the patient of this finding, all insulin was removed from the bottle and an equal volume of clear typhoid antigen substituted. The next morning the patient developed fever and chills with a large hot erythematous area appearing *locally at the site of injection*.

Rynearson[198] cites an instance wherein a patient underwent a total of 7 exploratory operations before the factitious nature of the hypoglycemia was discovered. He added radioactive phosphorus to the concealed insulin vial and the next day when the patient lapsed into unconsciousness due to hypoglycemia, a test of the urine revealed marked radioactivity.

We recently observed a similar patient with a five-year history of hypoglycemic attacks. Fasting blood sugar determinations were erratic, varying from 10 to 100 mg. per cent. The suspected vial of insulin was discovered in the patient's handbag when she left the room.

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Appendix

Chapter 35

LABORATORY TESTS OF ENDOCRINE FUNCTION

Chloride in Serum[1]

Reagents

1. Mercuric nitrate solution
   Dissolve 2.9 to 3.0 grams of mercuric nitrate (c.p. Baker's analyzed) in 200 ml distilled water
   Add 20 ml 2N nitric acid
   Dilute to 1000 ml with distilled water
2. Indicator—Diphenylcarbazone (Eastman Kodak #4459)
   Dissolve 100 mg diphenylcarbazone in 100 ml ethyl alcohol and store in a dark bottle in the refrigerator
   Prepare fresh each month
3. Standard sodium chloride solution
   Dry sodium chloride (c.p.) in oven overnight at 120° C
   Dissolve 584.5 mg of sodium chloride in distilled water and dilute to 1000 ml
   This solution contains 10 milliequivalents of Cl per liter
   To standardize mercuric nitrate solution titrate 2 ml of the standard sodium chloride solution

Procedure

Place 0.2 ml serum in a 25 ml Erlenmeyer flask
Add 1.8 ml distilled water
4 drops of indicator
Add mercuric nitrate from a microburette calibrated in 0.01 ml intervals (1 ml should equal about 100 drops)
The color of the mixture is a salmon red which changes to a deep violet when the end point has been reached
The removal of proteins intensifies the color change at the end point However deproteinization is not essential

Calculation

$$\frac{\text{titer of unknown}}{\text{titer of standard}} \times 0.02 \times \frac{1000}{0.2} = \text{milliequivalents of Cl/liter}$$

Normal values 98 to 110 milliequivalents/liter

Urinary Chloride

The method described above for the determination of serum chloride may be applied to urine

Sodium in Serum[2]

Reagents

1. Ashing mixture
   95 ml nitric acid (concentrated)

5 ml sulfuric acid (concentrated)
5 ml perchloric acid (70%)

2 Uranium zinc acetate reagent

Solution A

80 grams Na free uranium acetate $UO_2(C_2H_3O_2)_2 \cdot 2H_2O$
48 grams or 46 ml 30% acetic acid (% by volume)
Add water to 520 gram

Solution B

220 grams zinc acetate $Zn(C_2H_3O_2)_2 \cdot 2H_2O$
24 grams or 23 ml 30% acetic acid
Add water to 520 gram

Cover and warm both solutions on steam bath Stir occasionally until solution is complete Mix while hot

Let stand 24 hours before using

If no yellow precipitate appears add 0.2 gram of precipitated uranyl zinc sodium acetate to saturate solution

Shake solution occasionally

3 Ethyl alcohol 95% saturated with uranium sodium zinc acetate

4 Ethyl ether

Procedure

Pipette 1 ml serum into a 25 ml Erlenmeyer flask
Add 4 ml ashing mixture
Mix and heat carefully on a hotplate until one drop is left
Cool and add 1 ml distilled water
Mix thoroughly
Add 10 ml freshly filtered uranium zinc acetate solution
Mix thoroughly
Add another 10 ml portion of the reagent and mix
Let stand one hour

From a desiccator take a clean dry fritted glass filter and weigh on an analytical balance

Place filter on suction flask and transfer quantitatively the contents of the Erlenmeyer flask

Wash the Erlenmeyer with a 6 ml portion of the uranium zinc acetate reagent and transfer this to the filter

Wash filter with three 2 ml portions of freshly filtered alcohol saturated with uranyl sodium zinc acetate

Wash three times with 2 ml portions of ethyl ether

Dry with suction and place in desiccator over calcium chloride for ½ hour and then weigh

Run blank on all reagents simultaneously

Calculation

$$\frac{23}{1538} \times 100 = 1.495$$

1.495 × (mg of precipitate − mg of blank) = mg Na/100 ml

$$\frac{23}{1538} \times \frac{1}{23} \times 1000 = 0.65$$

0.65 × (mg of precipitate − mg of blank) = meq of Na/liter

Normal Values 137–142 meq/liter

Sodium in Urine[4,5]

Reagents

1. Uranium zinc acetate
2. Phenolphthalein—1% alcoholic solution
3. Powdered mercuric chloride
4. Powdered calcium hydroxide
5. Ethyl alcohol 95% saturated with uranium sodium zinc acetate
6. Ethyl ether

Procedure

Into a small Erlenmeyer flask, measure roughly about 6 ml urine

Add 1 drop phenolphthalein and 0.2 gram powdered $Ca(OH)_2$

Shake and let stand 30 minutes with occasional shaking. Solution should turn pink

If urine contains protein take about 10 ml urine and add 0.5 gram $HgCl_2$, and then add $Ca(OH)_2$

Filter through a fine paper and place a stopper in the test tube to avoid precipitation of $CaCO_3$ by CO_2 in atmosphere

If urine contains protein test filtrate. If protein is still present add more $HgCl_2$ and refilter

Fit a solid rubber stopper from below into the bottom of a fritted glass filter which has been dried in a desiccator and weighed

Pipette approximately 20 ml of freshly filtered uranium zinc acetate reagent into filter

Pipette 2 ml urine filtrate directly into reagent in filter

Stir with a small glass rod until precipitate appears

Continue stirring for a few minutes thereafter

Withdraw stirring rod rinsing it with 3 to 5 ml of the reagent

Cover filter with watch glass and let stand 1 hour

The temperature of the room should be kept fairly constant

Remove stopper and place filter on a suction flask

After reagent has been filtered off wash twice with 5 ml portions of freshly filtered alcohol saturated with uranium sodium zinc acetate

Wash sides of filter carefully

Wash twice with 5 ml portions of ethyl ether

Dry with suction and place in desiccator over calcium chloride for ½ hour. Weigh

Run a blank on all reagents simultaneously

Calculation

$$\frac{14.95 \times (\text{grams of precipitate} - \text{blank})}{V} = \text{grams of Na/l}$$

$$\frac{650 \times (\text{grams of precipitate} - \text{blank})}{V} = \text{meq/l of Na}$$

V = ml of urine in sample

Potassium in Serum[3]

Reagents

1. Sulfuric acid—4 normal
   112 ml sulfuric acid diluted to 1000 ml with distilled water

2 Thorium nitrate ($Th(NO_3)_4$) 10%
10 grams thorium nitrate dissolved in distilled water and diluted to 100 ml
3 Phosphoric acid (H_3PO_4)—0 1%
1 ml phosphoric acid—85% diluted to 850 ml with distilled water
4 Chloroplatinic acid ($H_2PtCl_6\ 6H_2O$) containing 10% platinum 26 5 grams of chloroplatinic acid dissolved in water and diluted to 100 ml
5 Absolute ethyl alcohol saturated with potassium chloroplatinate
Shake alcohol with a small quantity of the salt
6 10% potassium chloride saturated with potassium chloroplatinate
Shake potassium chloride with a small quantity of the salt
7 Potassium iodide (KI)—2 normal
33 2 grams potassium iodide dissolved in distilled water and diluted to 100 ml
8 Sodium thiosulfate ($Na_2S_2O_3$) 0 01 normal
Dilute from 0 1 N standardized against potassium biniodate

Apparatus

Muffle furnace
Platinum crucible
Shohl microfilter
Drop a small glass bead into a funnel with a 1 inch diameter and make a mat of fine-grained asbestos

Procedure

Pipette 1 ml serum into a platinum crucible
Add 2 drops 4N sulfuric acid
Mix thoroughly
Add 1 ml thorium nitrate
Rotate crucible carefully in order to mix the contents completely
Place on steam bath and evaporate to dryness
When dry place crucible on outer door of muffle furnace (which has previously been heated to 750 C) and slowly introduce it into the furnace
Close door of furnace and ash for 10 minute or until a snow white ash is obtained
Add 1 0 ml of the phosphoric acid (0 1%) to the ash and mix thoroughly with a small glass rod
Add a 5 ml portion of the phosphoric acid and again mix thoroughly
Transfer this 6 ml to a 15 ml conical centrifuge tube and centrifuge
Pipette a 5 ml aliquot into a 50 ml pyrex beaker
Place on a steam bath and evaporate to dryness
To beaker add
0 3 ml chloroplatinic acid
5 0 ml absolute alcohol
Mix and let stand 20 minutes
Place Shohl microfilter on a suction flask containing a test tube for collection of excess platinum solution (this may later be recovered)
Transfer quantitatively to the Shohl filter the contents of the beaker
Wash beaker with four 2 ml portions of freshly filtered absolute alcohol saturated with potassium chloroplatinate and pass through filter
Release suction and replace catch tube
Wash beaker with four 2 ml portions of freshly filtered potassium chloride saturated with potassium chloroplatinate and pass through filter
Remove filter funnel from suction flask and invert over the 50 ml beaker used previously
Insert glass rod into stem of funnel and return filter to beaker
Wash funnel with 1 to 2 ml hot distilled water

Add 1 ml. 2 normal potassium iodide and place on water bath at 65° C. for 15 minutes.

Titrate while still hot with 0.01 N thiosulfate from a microburette.

End point is a lemon yellow color free from red.

Run a blank on all reagents simultaneously.

Calculation:

$$\frac{10\,(A-B)}{C} = \text{meq of K/l}$$

$$\frac{39.1\,(A-B)}{C} = \text{mg. of K/100 ml.}$$

A = ml. of 0.01 thiosulfate used in titration of unknown
B = " " " " " blank
C = ml. of unknown

Normal Values: 3.5 to 4.5 meq/liter.

Potassium in Urine

Urine potassium may be determined by the same method used for serum.

THE USE OF THE FLAME PHOTOMETER FOR THE DETERMINATION OF SERUM AND URINARY SODIUM AND POTASSIUM

For the rapid determination of sodium and potassium, a flame photometer may be employed. Stock standards containing known concentrations of sodium chloride and potassium chloride are prepared, and from these solutions a curve is drawn. A solution of lithium chloride is also prepared for use as an internal standard, *i.e.*, the light of the element to be determined is directly compared to the light emitted by the lithium.

Stock standard:

All chemicals used should be of the highest chemical purity.

1. Dry sodium chloride and potassium chloride in an oven at 110° C. for several hours before weighing.

   Dissolve 1.4614 grams of sodium chloride and 1.8638 grams of potassium chloride in distilled water and dilute to 500 ml.

   This solution contains 25 mM. of sodium and potassium respectively and is used for dilutions of less concentrated standard.

2. *Dissolve 10.624 grams of lithium chloride in distilled water and dilute to 2000 ml.* This solution contains 250 mM. of lithium chloride.

Dilute the stock standard for working standards containing 1.0, 0.8, 0.6, 0.5, 0.4, 0.3, 0.2, and 0.1 mM. of sodium and potassium and 10 mM. of lithium chloride respectively.

A solution containing 10 mM. of lithium chloride is also made to be used for adjusting the zero point of the machine.

Total and Bound Magnesium in Serum[7,8,9]

Reagents:

1. Trichloracetic acid—20%
   20 grams trichloracetic acid dissolved in distilled water and diluted to 100 ml.
2. Sodium acetate—20%
   20 grams sodium acetate dissolved in distilled water and diluted to 100 ml.

3 Brom-cresol green
0.016% alcoholic solution
4 Ammonium hydroxide 1 1
Dilute 1 part ammonium hydroxide with 1 part distilled water
5 Ammonium hydroxide dilute
Dilute 1 part ammonium hydroxide with 50 parts distilled water
6 Ammonium oxalate saturated
(about 4%)
7 Potassium dihydrogen phosphate—2%
Dissolve 2 grams potassium dihydrogen phosphate in distilled water and dilute to 100 ml
8 Ammonia alcohol wash solution
Dilute 200 ml 85% alcohol and 50 ml concentrated ammonium hydroxide to 1000 ml with distilled water
9 Stock standard
Dissolve 560 mg potassium dihydrogen phosphate in distilled water and dilute to 1000 ml
Store in refrigerator
For working standard dilute 10 times
1 ml of working standard is equivalent to 0.01 mg of magnesium
10 Stannous chloride stock solution 40%
Dissolve 11.5 grams $SnCl_2 \cdot 2H_2O$ in 25 ml concentrated hydrochloric acid
Dilute 200 times immediately before using
11 Sodium molybdate 7.5%
Dissolve 7.5 grams sodium molybdate in distilled water and dilute to 100 ml
12 Sulfuric acid—10 normal
282 ml concentrated sulfuric acid are diluted to 1000 ml with distilled water

Procedure

In a 15 ml conical centrifuge tube place
3 ml serum
9 ml distilled water
3 ml 20% trichloracetic acid
Mix thoroughly and let stand one half hour
Centrifuge and filter supernatant fluid through a Whatman #42 filter paper
Into a clean 15 ml *conical centrifuge tube put*
10 ml filtrate
1 ml sodium acetate
1 ml *ammonium oxalate*
6-8 drops brom-cresol green
Mix with a stirring rod and adjust to pH 5.0 with the 1 1 ammonium hydroxide
Let stand overnight
Centrifuge and decant supernatant fluid into another 15 ml conical centrifuge tube
Wash precipitate once with a small amount of dilute ammonium hydroxide centrifuge and add wash to the original supernatant fluid
Add
1 ml potassium dihydrogen phosphate—2%
1 ml concentrated ammonium hydroxide
Stir well and let stand overnight
Centrifuge and decant supernatant fluid
Wash precipitate twice with ammonia alcohol wash solution
Centrifuge decant and place in drying oven at 90° to 95° C

Colorimetric assay

To dry precipitate add
- 1 ml 10 normal sulfuric acid
- 7 ml distilled water

Mix thoroughly and add
- 1 ml sodium molybdate
- 1 ml stannous chloride dilute

Mix and let stand at least 10 minutes and read in a photoelectric colorimeter using a blue filter with a maximal absorption at 420 mu

Standard solutions containing 0 01 and 0 02 mg plus a blank of the reagents are run simultaneously

Calculation

$$\frac{\text{Reading of unknown}}{\text{Reading of standard}} \times \text{Conc of standard} \times \frac{100}{2} = \text{mg of Magnesium/100 ml serum}$$

Normal values run between 2 and 3 mg 100 ml

For the determination of diffusible magnesium serum may be ultrafiltered through a #600 cellophane membrane according to the method described by Laviete [9]

The magnesium content is determined as described above except that it is unnecessary to precipitate the protein

In normal individuals the percentage of the total magnesium which is non diffusible does not exceed 25%

Individuals with hyperthyroidism show a very marked increase in the percentage of bound magnesium varying between 25 and 62% In myxedema the percentage of bound magnesium varies from 0 0 to 10%

Calcium Balance[10]

Place patient on a diet containing 100 mg of calcium per day for 6 days

Collect 24 hour samples of urine of the last 3 days of the diet period

Pool and analyze for calcium

An excretion of 300 mg or less of calcium for the 3 day period is considered normal In hyperparathyroidism considerably over 300 mg will be excreted

SAMPLE DIET

	Allow	Avoid
Soup	None	Omit entirely
Meat fish poultry 0 008 gram calcium	2 of following daily 60 grams lean beef 50 chicken 50 lamb 65 lean veal 80 turkey 70 halibut 60 codfish 50 mackerel	Use no other meats fish or poultry
Eggs		Omit entirely
Milk and milk products	30 grams decalcified butter daily	Omit all others

SAMPLE DIET—(Continued)

	Allow		Avoid
Vegetables	3 of following daily		Use no other
0 009 gram calcium	40 grams	peas	vegetables
	15	asparagus	
	65	summer squash	
	60	winter squash	
	75	potato	
	80	fresh tomato	
	80	cucumber	
	100	corn	
	100	egg plant	
	130	tomato juice fresh	
Potato Substitutes	1 of following daily		Avoid all others
	25 grams	dry rice	
	15	spaghetti	
0 003 gram calcium	15	macaroni	
	15	noodles (egg free)	
	30	hominy	
Fruits	4 of following daily		Avoid all others
	50 grams	cantaloupe	
0 00 gram calcium	50	cherries	
	50	grapefruit	
	0	plum	
	50	pineapple	
	50	apricot	
	60	pears	
	60	grapefruit juice	
	80	peach	
	100	banana	
	100	apple	
	100	watermelon	
	100	tomato juice fresh	
Cereals	None		
Beverage	Fluid intake should be constant throughout test period 1 cup coffee at breakfast 1 tea at luncheon 1 at supper Water may be had between meals		Avoid all other beverages
Bread 0 008 gram calcium	0 grams with each meal		
Miscellaneous	2 grams c p salt for use throughout entire day Sugar as desired		Avoid all other food

Colorimetric assay

To dry precipitate add
- 1 ml 10 normal sulfuric acid
- 7 ml distilled water

Mix thoroughly and add
- 1 ml sodium molybdate
- 1 ml stannous chloride dilute

Mix and let stand at least 10 minutes and read in a photoelectric colorimeter using a blue filter with a maximal absorption at 420 mu

Standard solutions containing 0 01 and 0 02 mg plus a blank of the reagents are run simultaneously

Calculation

$$\frac{\text{Reading of unknown}}{\text{Reading of standard}} \times \text{Conc of standard} \times \frac{100}{2} = \text{mg of Magnesium/100 ml serum}$$

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SAMPLE DIET

	Allow	Avoid
Soup	None	Omit entirely
Meat fish poultry 0 008 gram calcium	2 of following daily 60 grams lean beef 50 chicken 50 lamb 65 lean veal 80 turkey 70 halibut 60 codfish 50 mackerel	Use no other meats fish or poultry
Eggs		Omit entirely
Milk and milk products	30 grams decalcified butter daily	Omit all others

2 Potassium permanganate
To purify crystal
Dissolve 700 grams of crystalline potassium permanganate in 2,500 ml redistilled water using heat for solution. Filter through glass wool into a beaker placed in an ice bath stirring constantly.
Collect crystals on a Buchner funnel using a Whatman #42 filter paper.
Wash 5 times with cooled redistilled water.
Transfer to a large porcelain evaporating dish and dry overnight in an oven at 100° C.
It may be necessary to repeat this procedure once or twice.
a Potassium permanganate 1% solution
b Potassium permanganate 0.2 molar solution
31.6 grams of recrystallized reagent are dissolved in redistilled water and diluted to 1000 ml. Store in a brown bottle and filter through a fritted glass funnel if a precipitate forms.
3 Sulfuric acid 18 normal (Merck or Mallinckrodt c.p. analytical reagent low nitrogen)
Pour 17 ml concentrated sulfuric acid slowly into 20 ml redistilled water to make 34 ml of solution (use these proportions to make large volumes of solution).
4 Sulfuric acid 8 normal
216 ml concentrated sulfuric acid are diluted to 1000 ml with redistilled water.
5 Potassium carbonate 1 molar
Dissolve 138.2 grams of potassium carbonate in redistilled water and dilute to 1000 ml.
6 Oxalic acid saturated at 30° C
Dissolve 500 grams oxalic acid (Mallinckrodt) by heating to 90° in 400 ml redistilled water.
Filter while hot through a Whatman #1 fluted filter paper into a beaker placed in an ice bath. Stir constantly.
Filter crystals into a Buchner funnel through a Whatman #42 filter paper and wash five times with chilled redistilled water.
Keep crystals in the dark at room temperature in a brown bottle with sufficient water to make a saturated solution.
Immediately before use heat solution to 30° C.
7 Sodium nitrite 0.75 normal solution
1.3 grams sodium nitrite dissolved in redistilled water and diluted to 50 ml.
Make fresh every 2 weeks.
8 Urea 5 molar solution
300.3 grams urea dissolved in redistilled water and diluted to 1000 ml.
9 Arrowroot starch solution 1%
Rub 10 grams of arrowroot starch with a little redistilled water and pour with stirring into a 1000 ml of boiling redistilled water. Remove from flame at once and cool. Add 1 gram of salicylic acid as a preservative. This solution will keep indefinitely if stored in the refrigerator.
10 Potassium iodide 0.2%
Prepare fresh daily.
11 Sodium thiosulfate solution 0.001 normal
Approximately 26.5 grams of sodium thiosulfate are dissolved in redistilled water and diluted to 1000 ml.
Allow to stand 2 weeks in order that sulfur may be precipitated.
This is a stock solution and is approximately 0.1 normal.
Store in a dark bottle.

Sulkowitch Test for Urinary Calcium[11]

Reagent

2.5 grams of oxalic acid
2.5 grams of ammonium oxalate
5.0 ml of glacial acetic acid
Dilute to 150 ml with distilled water

Procedure

Collect a 24 hour sample of urine and note volume
To a 5 ml aliquot add 5 ml of the reagent
Let stand 2 to 3 minutes
When calcium is present in the urine a fine white precipitate is formed indicating a normal blood calcium level
The absence of a precipitate indicates the absence of urinary calcium and a blood calcium level of less than 7.5 mg %
The presence of a heavy precipitate indicates hypercalcemia
This test should not be performed after the ingestion of large amounts of fluid or after the ingestion of milk

Serum Precipitable Iodine[12, 13]

Apparatus

1 All Pyrex distilling apparatus
  A Digestion flask made from 1200 ml Kjeldahl flask the neck of which has been replaced with a ground glass joint
  B Distilling arm connecting the flask with the condenser by two male ground glass joints The capillary tube attached to the dropping funnel extends to within 80 mm of the bottom of flask A The cross arm from the center of the capillary to the center of the condenser tube is 135 mm long
  C Short coil condenser the water jacket of which measures 170 mm Below the water jacket is a dew cup
  D Receiving flask made by cutting off the top of a 250 ml Erlenmeyer flask At the base is joined a short horizontal side arm with a capacity of approximately 3 ml and calibrated at 2 ml
  E Thermometer 10 cm long and calibrated in 1 divisions from 120 to 200 attached by a heavy rubber band to the capillary tube of the distilling arm
2 Thermometer 35 cm long and graduated from 0 to 200
3 Antibumps 17 and 13 cm long Join a short length of glass tubing to an end of glass rod
4 Fisher burners
5 Electric hot plate
6 Sand bath
7 All glass wash bottle
8 Rehberg microburette

Redistilled water is used for preparing all reagents and for rinsing all glassware used in the determination

Reagents

1 Redistilled water
In a 12 liter round bottom distilling flask place 6 liters of distilled water and approximately 200 grams of either potassium carbonate or potassium hydroxide Connect flask with all glass joints to a condenser and heat on a sand bath Discard distillate until it is neutral to methyl red Replace alkali every 2 or 3 weeks

2 Potassium permanganate

To purify crystals

Dissolve 700 grams of crystalline potassium permanganate in 2500 ml redistilled water using heat for solution. Filter through glass wool into a beaker placed in an ice bath stirring constantly.

Collect crystals on a Buchner funnel using a Whatman #42 filter paper.

Wash 3 times with cooled redistilled water.

Transfer to a large porcelain evaporating dish and dry overnight in an oven at 100° C.

It may be necessary to repeat this procedure once or twice.

a Potassium permanganate 1% solution

b Potassium permanganate 0.2 molar solution

31.6 grams of recrystallized reagent are dissolved in redistilled water and diluted to 1000 ml. Store in a brown bottle and filter through a fritted glass funnel if a precipitate forms.

3 Sulfuric acid 18 normal (Merck or Mallinckrodt c.p. analytical reagent low nitrogen)

Pour 17 ml concentrated sulfuric acid slowly into 20 ml redistilled water to make 34 ml of solution (use these proportions to make large volumes of solution)

4 Sulfuric acid 8 normal

216 ml concentrated sulfuric acid are diluted to 1000 ml with redistilled water

5 Potassium carbonate 1 molar

Dissolve 138.2 grams of potassium carbonate in redistilled water and dilute to 1000 ml

6 Oxalic acid saturated at 30° C

Dissolve 500 grams oxalic acid (Mallinckrodt) by heating to 90° in 400 ml redistilled water

Filter while hot through a Whatman #1 fluted filter paper into a beaker placed in an ice bath. Stir constantly.

Filter crystals into a Buchner funnel through a Whatman #42 filter paper and wash five times with chilled redistilled water.

Keep crystals in the dark at room temperature in a brown bottle with sufficient water to make a saturated solution.

Immediately before use heat solution to 30° C

7 Sodium nitrite 0.75 normal solution

1.3 grams sodium nitrite dissolved in redistilled water and diluted to 50 ml

Make fresh every 2 weeks

8 Urea 5 molar solution

300.3 grams urea dissolved in redistilled water and diluted to 1000 ml

9 Arrowroot starch solution 1%

Rub 10 grams of arrowroot starch with a little redistilled water and pour with stirring into a 1000 ml of boiling redistilled water. Remove from flame at once and cool. Add 1 gram of salicylic acid as a preservative. This solution will keep indefinitely if stored in the refrigerator.

10 Potassium iodide 0.2%

Prepare fresh daily

11 Sodium thiosulfate solution 0.001 normal

Approximately 26.5 grams of sodium thiosulfate are dissolved in redistilled water and diluted to 1000 ml

Allow to stand 2 weeks in order that sulfur may be precipitated

This is a stock solution and is approximately 0.1 normal

Store in a dark bottle

Sulkowitch Test for Urinary Calcium[11]

Reagent

25 grams of oxalic acid
25 grams of ammonium oxalate
50 ml of glacial acetic acid
Dilute to 150 ml with distilled water

Procedure

Collect a 24 hour sample of urine and note volume
To a 5 ml aliquot add 5 ml of the reagent
Let stand 2 to 3 minutes

When calcium is present in the urine a fine white precipitate is formed indicating a normal blood calcium level

The absence of a precipitate indicates the absence of urinary calcium and a blood calcium level of less than 7 5 mg %

The presence of a heavy precipitate indicates hypercalcemia

This test should not be performed after the ingestion of large amounts of fluid or after the ingestion of milk

Serum Precipitable Iodine[12,13]

Apparatus

1 All Pyrex distilling apparatus
   A Digestion flask made from 1200 ml Kjeldahl flask the neck of which has been replaced with a ground glass joint
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   C Short coil condenser the water jacket of which measures 170 mm Below the water jacket is a dew cup
   D Receiving flask made by cutting off the top of a 250 ml Erlenmeyer flask At the base is joined a short horizontal side arm with a capacity of approximately 3 ml and calibrated at 2 ml
   E Thermometer 10 cm long and calibrated in 1° divisions from 120° to 200° attached by a heavy rubber band to the capillary tube of the distilling arm
2 Thermometer 35 cm long and graduated from 0° to 200°
3 Antibumps 17 and 13 cm long Join a short length of glass tubing to an end of glass rod
4 Fisher burners
5 Electric hot plate
6 Sand bath
7 All glass wash bottle
8 Rehberg microburette

Redistilled water is used for preparing all reagents and for rinsing all glassware used in the determination

Reagents

1 Redistilled water
   In a 12 liter round bottom distilling flask place 6 liters of distilled water and approximately 200 grams of either potassium carbonate or potassium hydroxide Connect flask with all glass joint to a condenser and heat on a sand bath Discard distillate until it is neutral to methyl red Replace alkali every 2 or 3 weeks

2. Potassium permanganate
   To purify crystals
   Dissolve 700 grams of crystalline potassium permanganate in 2800 ml. redistilled water using heat for solution. Filter through glass wool into a beaker placed in an ice bath, stirring constantly.
   Collect crystals on a Buchner funnel using a Whatman #42 filter paper.
   Wash 3 times with cooled redistilled water.
   Transfer to a large porcelain evaporating dish and dry overnight in an oven at 100° C.
   It may be necessary to repeat this procedure once or twice.
   a. *Potassium permanganate, 1% solution*
   b. Potassium permanganate, 0.2 molar solution
      31.6 grams of recrystallized reagent are dissolved in redistilled water and diluted to 1000 ml. Store in a brown bottle and filter through a fritted glass funnel if a precipitate forms.
3. Sulfuric acid, 18 normal (Merck or Mallinckrodt c.p. analytical reagent, low nitrogen)
   Pour 17 ml. concentrated sulfuric acid slowly into 20 ml. redistilled water to make 34 ml. of solution (use these proportions to make large volumes of solution).
4. Sulfuric acid, 8 normal
   216 ml. concentrated sulfuric acid are diluted to 1000 ml. with redistilled water.
5. Potassium carbonate, 1 molar
   Dissolve 138.2 grams of potassium carbonate in redistilled water and dilute to 1000 ml.
6. Oxalic acid saturated at 30° C.
   Dissolve 500 grams oxalic acid (Mallinckrodt) by heating to 90° in 400 ml. redistilled water.
   Filter while hot through a Whatman #1 fluted filter paper into a beaker placed in an ice bath. Stir constantly.
   Filter crystals into a Buchner funnel through a Whatman #42 filter paper and wash five times with chilled redistilled water.
   Keep crystals in the dark at room temperature in a brown bottle with sufficient water to make a saturated solution.
   Immediately before use heat solution to 30° C.
7. Sodium nitrite, 0.75 normal solution
   1.3 grams sodium nitrite dissolved in redistilled water and diluted to 50 ml.
   Make fresh every 2 weeks.
8. Urea, 5 molar solution
   300.3 grams urea dissolved in redistilled water and diluted to 1000 ml.
9. Arrowroot starch solution, 1%
   Rub 10 grams of arrowroot starch with a little redistilled water and pour with stirring into 1000 ml. of boiling redistilled water. Remove from flame at once and cool. Add 1 gram of salicylic acid as a preservative. This solution will keep indefinitely if stored in the refrigerator.
10. Potassium iodide, 0.2%
    Prepare fresh daily.
11. Sodium thiosulfate solution, 0.001 normal
    Approximately 25 grams of sodium thiosulfate are dissolved in redistilled water and diluted to 1000 ml.
    Allow to stand 2 weeks in order that sulfur may be precipitated.
    This is a stock solution and is approximately 0.1 normal.
    Store in a dark bottle.

Titrate with 0.001 normal sodium thiosulfate solution delivered from a Rehberg microburette

When the blue starch iodine color has almost disappeared chill the flask in ice water again

As the end point is approached not more than 0.0005 to 0.0008 ml. of thiosulfate should be added at once

During titration the tip of the burette should dip below the surface of the solution

Blank

The technic for the blank is the same except that the original digestion must be prolonged in order to get an equivalent reduction of the potassium permanganate and that after the evaporation of the distillate iodine must be added since the value is so low that accurate titration is not possible. Therefore before the oxidation of the 7 ml. of distillate 0.5 ml. of 0.00005 normal biiodate should be added

It is advisable to oxidize and titrate a mixture of

0.5 ml. of 0.00005 normal biiodate

1.0 ml. of 0.1 molar sodium bisulfite

1.0 ml. of 1.0 molar potassium carbonate

The value of the blank is the difference between the titers of the control iodate sample and the distillate to which the iodate was added

If the difference does not exceed 0.005 ml. of thiosulfate the reagents have been sufficiently purified

Calculation

$$\frac{100}{\text{Ml serum used}} \times \frac{T - Bl}{0.0473} = \gamma \text{ iodine/100 ml. serum}$$

T = observed titer corrected for burette calibration and thiosulfate factor

Bl = titer of blank corrected for burette calibration and thiosulfate factor

0.0473 = ml. of 0.001 normal thiosulfate equivalent to 1 γ of iodine

A value of 4 to 8 γ% is considered normal

A value above 9 γ% is found in hyperthyroidism

A value of less than 4 γ% is found in hypothyroidism

Urinary Excretion of Radioactive Iodine[14]

Administer orally 100 microcuries of radioiodine (I^{131}) to the patient

Collect a 24 hour sample of urine and note the volume

Measure the amount of radiation in a 100 ml. aliquot using an immersion type shielded gamma counter calibrated against a standard sample of iodine

Excretion of less than 20% in individuals having adequate renal function is consistent with the diagnosis of Graves' disease

Excretion of from 20 to 30% is considered equivocal while an excretion of over 35% in the absence of antithyroid medication is considered normal

Urinary Neutral 17 Ketosteroids[15,16,17,18,19]

Reagents

1. Hydrochloric acid concentrated (HCl)
2. Stannous chloride ($SnCl_2$)
3. Carbon tetrachloride (CCl_4)
4. Ethyl ether

(Place 2 large antibumps and a 200° thermometer in the flask, which is supported on an asbestos wire gauze on a ring stand.)
Apply gentle heat from a Fisher burner, shaking flask until boiling commences
If foaming is excessive, stop heat and add a little water from a wash bottle
When mixture boils steadily, no further shaking is necessary and heat may be increased
Continue digestion until a temperature of 195° is reached (about 25 to 30 minutes)
When the digest has cooled to below 100°, add 1.0 ml of the 1% potassium permanganate solution
Reheat to 145° shaking constantly
When digest has again cooled to below 100° remove thermometer, washing it with about 25 ml of redistilled water

Distillation

Connect digestion flask to still
In receiving flask place 1 ml each of 1.0 molar potassium carbonate and 0.1 molar sodium bisulfite and tilt it so that the tip of the condenser dips below the surface of the fluid
Apply heat until the digest becomes 138° to 140°
Introduce saturated oxalic acid through dropping funnel slowly enough that the rate of the evolution of carbon dioxide is moderate and that the temperature does not fall below 135°
Decolorization of digest indicates complete reduction, although a few minutes may be required for the disappearance of some black specks
To insure complete liberation of iodine, 2 to 3 ml excess oxalic acid should be added. A greater excess is inadvisable
Continuous shaking and the addition of water is necessary during the reduction of the digest
Collect about 170 ml of distillate over a period of at least 30 minutes
Remove receiving flask, add a small antibump and place on a hot plate
Evaporate distillate to approximately 20 ml
Wash and remove antibump and continue evaporation slowly (to prevent spattering) to about 6 to 7 ml

Oxidation

Place flask in a shallow 70° to 80° water bath on a hot plate and add 8 drops of 0.2 molar potassium permanganate solution
If these are decolorized, add more of the permanganate until a permanent purple color is attained
After 4 minutes add 10 drops of 8 normal sulfuric acid
(Carbon dioxide is evolved but the purple color should persist.)
After another 4 minutes remove flask from water bath and add 0.75 normal sodium nitrite solution dropwise and with continuous shaking, until the solution is water-clear and no specks of manganese dioxide remain
Add 1 excess drop of sodium nitrite and wash sides of flask by carefully rotating it
Add 2 drops of 5 molar urea and again wash sides of flask carefully
The addition of the nitrite and the urea should take about a minute and a half
Replace flask in water bath until the solution reaches a volume of about 2.0 ml
(This volume should be constant in all the determinations.)

Titration

Chill flask in ice water and add 1 drop of the starch solution and 0.06 ml of freshly prepared 0.2% potassium iodide solution
Mix by rotation

For working solution, dilute 1 ml. of stock solution to 100 ml. with redistilled water. Prepare fresh at least once every two weeks and store in the refrigerator.

To standardize:

Into an Erlenmeyer flask pipette:

2 ml. of 0.01 normal biiodate solution

1 ml. potassium iodide 1%

Cool in ice water.

Add 10 drops sulfuric acid (8 normal) and titrate immediately with 0.001 normal sodium thiosulfate solution delivered from a 50 ml. burette calibrated at 0.1 ml. intervals.

When the yellow color has almost disappeared, add 6 drops of 1% starch solution and continue titration until the blue starch-iodine color disappears.

The thiosulfate factor is obtained thus:

$$\frac{2.00}{\text{Observed titer}} = \text{factor of thiosulfate}$$

12. Biiodate solution, 0.1 normal.

3.250 grams of potassium biiodate are dissolved in redistilled water and diluted to 1000 ml.

13. Solution A.

Zinc sulfate.

12.5 grams $ZnSO_4 \cdot 7H_2O$ are dissolved in redistilled water; add 125 ml. of 0.25 normal sulfuric acid. Dilute to 1 liter with redistilled water.

Solution B.

0.75 normal sodium hydroxide.

3 grams of sodium hydroxide are dissolved in redistilled water and diluted to 1000 ml.

Balance solutions A and B so that 6.70 to 6.80 ml. of the sodium hydroxide are required to produce a permanent pink color with 50 ml. of the zinc sulfate solution using phenolphthalein as an indicator. The sodium hydroxide must be added slowly and with continuous shaking.

Procedure

All determinations and blanks are carried out in duplicate.

In an Erlenmeyer flask mix:

6 ml. serum

48 ml. zinc sulfate solution

6 ml. sodium hydroxide 0.75 normal

Filter through a Whatman #42 filter paper.

Wash precipitate 8 to 12 times with redistilled water, stirring precipitate with a blunt stirring rod.

(Test washings with dilute acidified silver nitrate solution, washing precipitate with water until no silver chloride precipitate appears.)

Transfer the precipitate with the filter paper to the digestion flask.

Digestion

Add 15 grams recrystallized potassium permanganate.

Slowly introduce about 40 ml. of 18 normal sulfuric acid.

Shake vigorously.

When violent foaming has subsided, add another 40 ml. portion of the sulfuric acid.

A total of 210 ml. of the acid should be added.

5 10% sodium hydrosulfite ($Na_2S_2O_4$) in 1 N sodium hydroxide
  10 grams sodium hydrosulfite diluted in 1 normal sodium hydroxide and diluted to 100 ml

6 1 normal sodium hydroxide (NaOH)
  40 grams NaOH dissolved in distilled water and diluted to 1000 ml

7 0.5 normal hydrochloric acid
  41 ml concentrated hydrochloric acid diluted to 1000 ml with distilled water

8 Glacial acetic acid (CH_3COOH)

9 Girard's reagent T

10 Sodium hydroxide 10%
  10 grams sodium hydroxide dissolved in distilled water and diluted to 100 ml

11 Sulfuric acid concentrated (H_2SO_4)

12 Absolute ethyl alcohol

13 Ethyl alcohol 95%

14 Sodium hydroxide 2 normal
  80 grams sodium hydroxide dissolved in water and diluted to 1000 ml

15 Meta-dinitrobenzene
  11.6 mg/ml absolute alcohol. Store in brown bottle in refrigerator. This solution remains stable for 10 to 14 days.

  To purify meta-dinitrobenzene
  Dissolve 20 grams of extra pure meta-dinitrobenzene (M.P. 89–89.5°) in 750 ml 95% ethyl alcohol
  Warm to 40° and add 100 ml 2 normal sodium hydroxide
  Cool after 5 minutes and add 2500 ml distilled water
  Collect precipitate in a Buchner funnel
  Wash thoroughly with water and dry with suction
  Recrystallize from 120 and 80 ml absolute alcohol
  The colorless needles thus obtained should have a melting point of 90.5 to 91
  Mix a 1% alcoholic solution of meta-dinitrobenzene with an equal volume of 2 normal sodium hydroxide. This should remain colorless after an hour.

16 Potassium hydroxide (KOH) 2.5 normal alcoholic solution
  Dissolve with the aid of mechanical stirring about 9 grams KOH in 50 ml absolute ethyl alcohol
  Filter with suction through a hard filter paper (Whatman #50)
  To check concentration titrate with 0.5 normal sulfuric acid using methyl orange as an indicator and adjust with alcohol if necessary to bring the solution to the limits of 2.48 to 2.52 normal. Store in refrigerator. This solution is stable for 2 to 5 days.

17 Acetone

18 Digitonin 7 mg/ml
  Make a mg/ml aqueous solution of digitonin. Let stand overnight and filter
  Concentrate to 7 mg/ml by evaporation on steam bath

19 Benzene

Procedure

Collect a 24 hour urine specimen using 7 ml concentrated hydrochloric acid as a preservative

Measure volume of urine and add 150 ml concentrated hydrochloric acid for each liter of urine

Add 0.7 gram stannous chloride to prevent emulsion

Heat to 80° over a flame, and transfer to continuous extractor using carbon tetrachloride as a solvent

Titrate with 0 001 normal sodium thiosulfate solution delivered from a Rehberg microburette

When the blue starch iodine color has almost disappeared, chill the flask in ice water again

As the end point is approached not more than 0 0005 to 0 0008 ml of thiosulfate should be added at once

During titration the tip of the burette should dip below the surface of the solution

Blank

The technic for the blank is the same except that the original digestion must be prolonged in order to get an equivalent reduction of the potassium permanganate and that after the evaporation of the distillate iodine must be added since the value is so low that accurate titration is not possible Therefore before the oxidation of the 7 ml of distillate 0 5 ml of 0 00005 normal biiodate should be added

It is advisable to oxidize and titrate a mixture of

0 5 ml of 0 00005 normal biiodate

1 0 ml of 0 1 molar sodium bisulfite

1 0 ml of 1 0 molar potassium carbonate

The value of the blank is the difference between the titers of the control iodate sample and the distillate to which the iodate was added

If the difference does not exceed 0 005 ml of thiosulfate the reagents have been sufficiently purified

Calculation

$$\frac{100}{\text{Ml serum used}} \times \frac{\text{T Bl}}{0\,0473} = \gamma \text{ iodine/100 ml serum}$$

T = observed titer corrected for burette calibration and thiosulfate factor

Bl = titer of blank corrected for burette calibration and thiosulfate factor

0 0473 = ml of 0 001 normal thiosulfate equivalent to 1 γ of iodine

A value of 4 to 8 $\gamma\%$ is considered normal

A value above 9 $\gamma\%$ is found in hyperthyroidism

A value of less than 4 $\gamma\%$ is found in hypothyroidism

Urinary Excretion of Radioative Iodine[14]

Administer orally 100 microcuries of radioiodine I^{131} to the patient

Collect a 24 hour sample of urine and note the volume

Measure the amount of radiation in a 100 ml aliquot using an immersion type shielded gamma counter calibrated against a standard sample of iodine

Excretion of less than 20% in individuals having adequate renal function is consistent with the diagnosis of Graves disease

Excretion of from 20 to 30% is considered equivocal while an excretion of over 35% in the absence of antithyroid medication is considered normal

Urinary Neutral 17 Ketosteroids[15 16 17 18 19]

Reagents

1 Hydrochloric acid concentrated (HCl)
2 Stannous chloride ($SnCl_2$)
3 Carbon tetrachloride (CCl_4)
4 Ethyl ether

Combine ether extracts and evaporate to dryness on a steam bath
Dissolve residue in absolute ethyl alcohol to original volume of aliquot portion used, and proceed with colorimetric determination

Precipitation of Dehydroisoandrosterone
Into a 15 ml conical centrifuge tube pipette
3 ml alcoholic extract
1 ml acetone
4 ml aqueous digitonin solution
Shake and let stand stoppered overnight
Centrifuge at 2000 r p m for 15 minutes
Pipette an aliquot portion into a stoppered bottle and add 25 ml benzene
Shake vigorously
Allow a short period for partial separation of the aqueous-benzene phase and then decant about four fifths of the supernatant fluid through a soft filter paper
Pipette 20 ml of this into a distilling flask and evaporate to dryness on a steam bath with the partial aid of a vacuum
Add 20 ml ethyl ether and again evaporate to dryness
Dissolve residue in a measured amount of absolute ethyl ether and determine colorimetrically

Urinary Neutral 17 Ketosteroids (Alternate Method)[50]

Reagents
1 Ethyl ether—redistilled and free from peroxides
To remove peroxides wash ether with a 1% aqueous solution of ferrous sulfate and then with distilled water Dry over anhydrous sodium sulfate
2 Hydrochloric acid—concentrated
3 Sodium carbonate 9%
4 Sodium hydroxide 10%
5 Redistilled ethyl alcohol—95% aldehyde free
6 M-dinitrobenzene 2% in 95% alcohol
This solution is stable for 10 days
7 Potassium hydroxide 5 normal aqueous solution
28 05 grams potassium hydroxide dissolved in 100 ml distilled water
Test each new lot of potassium hydroxide solution for carbonate precipitation by adding 10 4 ml of 95% alcohol to 0 2 ml of the potassium hydroxide
Seal solution with parrafin
This solution is stable for a month
Collect a 24 hour sample of urine and note volume

Procedure
Place a 100 ml aliquot of urine in an Erlenmeyer flask
Add 10 ml concentrated hydrochloric acid
Place on a hot plate and boil for 15 minutes
Cool in ice bath
Transfer to a separatory funnel and shake 3 times for 5 minutes each time with 75 50 and 25 ml portions of ethyl ether
Combine ether extracts in a separatory funnel and wash
Once with 25 ml of distilled water
Twice lots of sodium carbonate 9%
sodium hydroxide 10%
3 times distilled water

Extract for 7 hours
Distil carbon tetrachloride (this may be used again) and dissolve residue in 100 ml ethyl ether
Transfer ether to a separatory funnel and
Wash twice with 25 ml portions $Na_2S_2O_4$—10% in 1 normal NaOH
" " " " " " 1 Normal NaOH
" " " 0 5 normal HCl
" 3 times " " " distilled water

Evaporate ether to dryness on steam bath and dissolve residue in absolute alcohol using 1 ml alcohol for each 100 ml of urine extracted
This is the crude extract

Colorimetric Determination
Clean all colorimetric tubes with a nitric and chromic acid mixture
Into a series of colorimeter tubes
Measure carefully with a micropipette 0 1 and 0 2 ml of the crude extract (If less than 0 2 ml is used bring volume to 0 2 ml with absolute alcohol)
Add 0 2 ml meta-dinitrobenzene solution
0 2 ml 2 5 normal KOH
Shake thoroughly
Prepare two blanks simultaneously using
0 2 ml absolute alcohol
0 2 ml meta-dinitrobenzene solution
0 2 ml 2 5 normal KOH
Place in water bath at 25 ± 0 2 in dark for 80 minutes
Remove from water bath and add 20 ml 95% ethyl alcohol
Read in a darkened room in a photoelectric colorimeter within 3 to 20 minutes using first a green filter #520 and then a blue filter #420 To one of the blanks add a volume of the crude extract equal to the volume used in the test sample and read in the colorimeter immediately Subtract this reading from the reading of the unknown to correct for the color of the extract
The 17 ketosteroid content of the test substance is determined in terms of androsterone by reference to a calibration curve which has previously been constructed from measurements of known amounts of androsterone
If the reading obtained by the green filter is 1 5 times or more greater than that obtained by the blue filter the Girard separation is unnecessary

Girard Separation
Pipette an aliquot portion of the crude extract into a 250 ml Erlenmeyer flask and evaporate to dryness on a steam bath
Add 0 5 ml glacial acetic acid
200 mg Girard s reagent T
Stopper with tinfoil and heat on steam bath for 10 minutes
Cool and add 40 ml ice water
3 ml NaOH 10%
Extract 4 times with 40 ml portions of ethyl ether
Wash combined ether extracts 3 times with 20 ml portions of distilled water
To original aqueous phase plus the water washings of the ethereal extracts add
1 ml H_2SO_4 (concentrated)
20 ml ethyl ether
Let stand 2 hours or more
Add 1 ml H_2SO_4
Extract 4 times with 40 ml portions of ethyl ether

The urine residue is dissolved in 1.12 ml. of alcohol and this solution is run slowly drop by drop from a pipette into the 10% glucose solution, the tube being shaken continuously during the addition of this material. The original tubes are rinsed out with water which is added to the extract and the final volume is made up to 11.2 ml. with water. The extracts may be kept for 24 to 48 hours at ice-box temperature.

Method

Male white mice weighing 20 to 25 grams are used. As the response to adrenal cortical extracts may vary with different strains of mice, it is important to keep to the same strain.

Two days before adrenalectomy the mice are removed from their stock fare and placed on the McCollum lactation diet which contains 26% protein and 52% carbohydrate.

The animals are anesthetized with nembutal or ether and are bilaterally adrenalectomized by the usual lumbar route.

Following adrenalectomy they are placed in a constant temperature room or box at 76° C. and are maintained on the McCollum diet. 0.9% NaCl containing 5% glucose is given as drinking water on the first postoperative day, and 0.9% NaCl is substituted throughout the remainder of the test. The giving of glucose immediately following adrenalectomy almost completely eliminates the mortality due to operative shock.

On the third postoperative day food is removed at 5 P.M. and the mice are fasted until the following morning, at which time the drinking water is also removed.

On the fourth postoperative day, beginning at 9:15 A.M., a total of 7 injections are given at 9:15 A.M., 10 A.M., 10:45 A.M., 11:30 A.M., 12:30 P.M., 1:30 P.M., and 2:30 P.M. The material to be tested is taken into solution in 5% glucose and 10% alcohol. Two-tenths ml. are given subcutaneously for each injection containing 70 mg. of glucose.

At 3:30 P.M. the mice are weighed and anesthetized with sodium amytal (0.2 ml. of a 1.8% solution). The livers are quickly removed and plunged into 4 ml. of hot 30% KOH contained in a 15 ml. graduated centrifuge tube.

The tubes are heated in a boiling water bath and frequently shaken until all the tissue is in solution.

The glycogen is precipitated by the addition of 1.2 volumes of 95% alcohol. The tubes are heated until the mixture just begins to boil, cooled in an ice bath and centrifuged.

The supernatant liquid is poured off and the tubes are allowed to drain.

The sides of the tubes are washed down with 0.5 ml. alcohol and again allowed to drain. Final traces of alcohol are expelled by heating the tubes for a few minutes in a hot water bath.

The glycogen is hydrolyzed and the glucose is determined.

The glycogen is expressed in terms of mg. of liver glucose per 100 grams of mouse body weight.

Standard

The reference standard is 11-dehydro-17-hydroxycorticosterone (crystalline Compound E of Kendall).

The biologic activity equivalent to that of one microgram of 11-dehydro-17-hydroxycorticosterone in terms of amount of glycogen deposited is defined as one glycogen unit.

Normal Values

Adult females—25 to 55 glycogenic units per 24 hours.
Adult males —40 to 85 " "
In infants normal adult levels are attained after the age of two and one-half

Take ether extracts to dryness and prepare for colorimetry as above with the exception however that the incubation of color in the water bath takes only 45 minutes

Biologic Assay of the Urinary Adrenal Corticoids [1]

Reagents

1 Male white mice weighing 20 to 25 grams
2 5 and 10% glucose
3 Alcohol 10%
4 Potassium hydroxide 30%
5 Alcohol 95%
6 Hydrochloric or sulfuric acid
7 Ethylene dichloride
8 Chloroform
9 Sodium hydroxide, 0 1 normal
10 Nitrogen
11 11-dehydro 17 hydroxycorticosterone (crystalline Compound E of Kendall)

Procedure

Preparation of urinary extracts

For urines containing a normal or low titer of glycogenic activity a complete 48 hour specimen is necessary for assay

For urines containing a high titer a 24 hour specimen is sufficient

The urine is adjusted to pH 1 0 with hydrochloric or sulfuric acid and extracted 3 or 4 times with ethylene dichloride Chloroform may also be used If any emulsions are formed they may be broken by centrifugation or by allowing the mixture to stand for an hour

The clear ethylene dichloride extract is evaporated almost to dryness under reduced pressure the temperature of the water bath not exceeding 50 C

The residue is taken up in 30 ml of chloroform and the chloroform is extracted 3 times with 5 ml of cold 0 1 normal sodium hydroxide and 3 times with water

These washings are reextracted with chloroform

The combined chloroform is evaporated down to a volume of approximately 1 to 2 ml and is transferred to a test tube with small amounts of chloroform

The test tube is placed in a water bath at 50 C and the remainder of the chloroform is evaporated under a stream of nitrogen

The dry residue is stored in the cold until ready for assay

Preparation of extract for assay

6 to 8 mice are used for each assay For normal male urine the equivalent of six hours of urine is administered to each mouse whereas for normal female urine or urines expected to be low in glycogen activity the equivalent of eight hours of urine is given to each animal

The following will illustrate the manner in which the residue is prepared for assay so that the final extract will contain 10% alcohol plus the required amount of glucose which is approximately 70 mgm per mouse The addition of this amount of glucose aids in sharpening the sensitivity of the test For example the residue obtained from a 48 hour urine specimen is to be assayed on eight mice Each mouse receives seven injections of 0 2 ml so that the final extract is made up to 7 × 0 2 × 8 = 11 2 ml and should contain 70 × 8 = 560 mg of glucose A 10% glucose solution is accurately prepared and 5 6 ml of this solution is measured into a 15 ml graduated tube

Assay

On the night before the assay is to be done dissolve the dry residue in 3 ml glacial acetic acid

Two aliquots of the glacial acetic acid extract are taken for assay one sample is treated with the periodic acid reagent to form formaldehyde This is called the oxidized sample In the second sample the reaction is prevented by the addition of the stannous chloride reagent prior to the periodic acid reagent This is known as the unoxidized sample A blank of all the reagents is also run simultaneously and is treated in the same manner as the unoxidized sample

Oxidized Sample	*Unoxidized Sample*	*Reagent Blank*
In a 50 ml boiling flask 0 5 ml acetic acid extract 8 5 ml distilled water 0 5 ml periodic acid reagent Let it stand at room temperature for exactly 30 minutes Then arrest oxidation by the addition of 0 5 ml stannous chloride reagent	In a 50 ml boiling flask 0 5 ml acetic acid extract 8 5 ml distilled water 0 5 ml stannous chloride Mix thoroughly 0 5 ml periodic acid reagent	In a 50 ml boiling flask 0 5 ml glacial acetic acid 8 5 ml distilled water 0 5 ml stannous chloride Mix thoroughly 0 5 ml periodic acid reagent

Distillation

The outlet of the still is placed under the meniscus of 1 0 ml distilled water in a 10 ml volumetric flask

The reagent blank oxidized and unoxidized samples are then boiled over a microflame until approximately 8 ml of distillate are collected These distillates are then diluted to the 10 ml volume with distilled water

Colorimetric Assay

In a Klett colorimeter tube place
3 ml distillate
5 ml chromotropic acid reagent

Mix thoroughly and place in a boiling water bath for exactly 30 minutes

Cool rapidly to 25 and make up to 10 ml with 9 molar sulfuric acid

Mix cool and read in Klett-Summerson photoelectric colorimeter at 570 millimicrons

Subtract the reading of the unoxidized sample from that of the oxidized and refer to a calibration curve prepared from the oxidation and colorimetry of desoxycorticosterone dissolved in glacial acetic acid

Normal range 1 to 2 mg /24 hours

The Pituitary Adrenocorticotrophic Hormone Test for Adrenal Cortical Insufficiency [3]

Procedure

No food is permitted after 8 P M On the following day 200 ml of water are given at 6 A M 8 A M and 10 A M The urine is collected from 6 A M to 8 A M and an eosinophile count is done on the blood at 8 A M Immediately thereafter 25 mg of adrenocorticotrophic factor is injected intramuscularly

Urinary Corticosteroids[22]

Reagents

1 Chloroform redistilled in an all glass still

2 Glacial acetic acid Eimer and Amend R

3 Sodium sulfite, anhydrous

4 Sodium hydroxide 0 1 normal
4 grams sodium hydroxide made up to 1000 ml in distilled water

5 Periodic acid reagent 0 03 molar in 0 25 molar sulfuric acid
0 69 grams potassium periodate dissolved in 100 ml 0 25 molar sulfuric acid

6 Stannous chloride reagent
Dissolve 3 grams stannous chloride in 10 4 ml hot concentrated hydrochloric acid Dilute to 50 ml with distilled water Add tin shot for stability Discard when turbid

7 Chromotropic acid reagent
Dissolve 200 milligrams chromotropic acid (1 8-dihydroxynapthalene-3 6 disulfonic acid) in 4 ml distilled water in a 100 ml volumetric flask Dilute to volume with 15 molar sulfuric acid Prepare fresh daily
To recrystallize chromotropic acid
Dissolve by warming 10 grams chromotropic acid in 25 ml distilled water Add approximately 1 gram charcoal Heat on steam bath for 15 minutes Add a small amount of sodium sulfite and a few drops of concentrated hydrochloric acid
Filter through infusorial earth and wash with a few ml of distilled water
Remove filter and warm on steam bath slowly adding 200 ml acetone
Cool and filter

8 Approximately 9 M sulfuric acid
Dilute 500 ml sulfuric acid to 1000 ml with distilled water

9 Approximately 15 M sulfuric acid
Dilute 833 ml sulfuric acid to 1000 ml with distilled water

Collect a 24 hour urine sample using 5 ml chloroform as a preservative The sample should be kept cool during collection period

Procedure

Take a 200 ml aliquot and bring it to pH 1 0 by the addition of 20 ml concentrated hydrochloric acid

Transfer to a separatory funnel

Add 100 ml chloroform and shake hard for 5 minutes

Let stand until there is a complete separation of the urine and chloroform and draw off the chloroform layer into a 500 ml Erlenmeyer flask

Add 3 more 100 ml lots of chloroform shaking 5 minutes each time

Allow the pooled chloroform extracts to stand until any urine that has been dissolved in it rises to the top Siphon off the layer of urine

Add sodium sulfate to the pooled chloroform extracts Mix cover and allow to stand until the emulsion has been broken

Filter through a Whatman #5 filter paper

Chill the clear extract and wash

Twice with 0 1 its volume of 0 1 normal sodium hydroxide
Once " 0 1 " distilled water
Back wash each time with an equal volume of chloroform

Transfer washed chloroform extract to a distilling flask and evaporate under vacuum at a temperature not exceeding 50 When the extract has distilled down to about 10 ml transfer it quantitatively to a 125 ml standard taper Erlenmeyer flask and take it to complete dryness under vacuum

This dry residue is stable at room temperature

disease If on the other hand the volume of the largest hourly morning specimen is less than that of the night urine Addison's disease may or may not be present and the second half of the procedure is then performed as follows

The plasma collected above is analyzed for urea and chloride and similar determinations are performed on the nocturnal urine specimen

The following formula is then used to compute the result

$$X = \frac{\text{Urea in urine (mg \%)}}{\text{Urea in plasma (mg \%)}} \times \frac{\text{Chlorides in plasma (mg \%)}}{\text{Chlorides in urine (mg \%)}} \times \frac{\text{Volume of day urine (largest hourly specimen cc)}}{\text{Volume of night urine (total cc)}}$$

If the value of "X" in this equation is greater than 30 the patient probably does not have Addison's disease

If the value of "X" is less than 25 the patient probably has Addison's disease provided that nephritis has been excluded

Salt Deprivation Tests

Harrop Weinstein Soffer and Trescher[24]

The patient is given a salt free diet that is one containing less than 0 7 gram of sodium daily Control samples of blood are analyzed for sodium chlorides potassium urea nitrogen and hematocrit A 24 hour control urine specimen is obtained and the sodium content determined The patient is kept on this diet for 48 to 96 hours and the above data is repeated daily On such a diet the patient with Addison's disease behaves in a characteristic fashion There occurs an increase in the excretion of urinary sodium in excess of the intake a progressive and definite fall in blood sodium and chlorides an increase in urea nitrogen and blood potassium and an increase in the hematocrit This definite sequence of events is observed to occur only in Addison's disease Normal individuals and patients with other illnesses can be kept for prolonged periods of time on a salt free diet without manifesting any of the typical changes seen in patients with destructive lesions of the adrenal cortex

Actually it is not necessary to do the multitude of determinations outlined above as a provocative test The demonstration of an increase in the excretion of urinary sodium above the intake or a definite fall in the level of the blood sodium renders the diagnosis of Addison's disease conclusive

The test however is not without hazard since the patient with Addison's disease may be precipitated into a state of crisis upon the prolonged withdrawal of salt The test therefore should only be performed in the hospital The patient must be carefully observed and an adequate amount of potent cortical extract and intravenous salt must be immediately available for use if indicated

Cutler Power and Wilder Modification[26,27]

The patient is given a diet with a standard amount of sodium chloride and potassium In addition potassium citrate and water are administered in proportion to the body weight The test is terminated after a 52 hour period and the urine voided during the last 4 hour period is analyzed for its concentration of chlorides Under these circumstances patients with adrenal cortical insufficiency excrete urine with a high concentration of chlorides

This test differs from the original salt deprivation test only in that the concentration of chlorides rather than that of sodium is determined in the urine The patient is of course subjected to the same hazards

The urine is then collected from 9 A M to 12 noon and an eosinophile count is again done at 12 noon

The two urine specimens are analyzed for uric acid and creatinine and the uric acid creatinine ratio is computed and the per cent decrease of circulating eosinophiles is determined

The adrenocorticotrophic factor is available in powder form, the solubility of which varies with different batches The hormone is generally soluble in normal saline This solution should not be kept longer than 12 hours at 4 C nor for longer than 2 hours at room temperature

The following technic is recommended for direct eosinophile counts

The special diluting fluid used consists of

1% eosin 5 ml
Acetone 5 ml
Distilled water to 100 ml

The diluent is filtered before use Oxalated blood is drawn into a white count pipette up to the 1 mark and the special diluting fluid is then used in the usual fashion The pipette is shaken and the counting chamber is filled immediately The eosinophiles which stand out as red dots are counted after 3 minute

The average of 4 chambers is computed

Alternate Diluting Fluid

Stock Solutions

A 0 1% methylene blue in propylene glycol
B 0 1% phloxine in propylene glycol

Working Solutions

Mix {Dilute 2cc Solution A with 2cc distilled water
{Dilute 2cc Solution *B* with 2cc distilled water

Allow pipette containing diluted blood to stand at least 15 minutes before counting

The advantages of this method are that the eosinophile count need not be carried out at once and that a simultaneous total white blood cell count can be made

Interpretation

Patients with Addison s disease show little or no drop in the eosinophile count while in normal subjects there occurs a 70% or more reduction in eosinophile A 50% reduction is considered the lower limit of normal

In normal individuals following the injection of adrenocorticotrophic factor there occurs an approximately 100% increase in the uric acid-creatinine ratio Patients with Addison s disease show approximately a 20% increase An increase of over 50% is *evidence against adrenal insufficiency*

Water Tolerance Tests [4]

The day before the test the patient is maintained on a regular diet from which extra salt is omitted After the evening meal at 6 P M no further food or drink is permitted, except that indicated as part of the test At 10 30 P M the patient is asked to void and the urine is discarded All urine voided from this point until 7 30 the following morning is collected measured and saved for chemical analysis At 8.30 A M the patient again voids and the urine is discarded He is then given 20 ml of water per kilogram of body weight over a 45 minute period He again voids at 9.30 10 30 11 30 A M and at *12 30 P M Each specimen is collected and measured* At 11.30 A M blood is withdrawn under oil for chemical analysis If the volume of any single specimen voided during the morning is greater than the total volume of urine voided during the night such a response indicates the absence of Addison s

pressure If the proper plane has been entered the oxygen will bubble freely under this small amount of head pressure From 250 to 900 cc of oxygen is employed for visualization depending on the size of the patient and the size of the perirenal space The average amount usually employed is approximately 500 cc

The needle is removed after the introduction of the oxygen and the puncture site is coated with collodion The patient is then asked *to sit up and perform rowing* exercises for about 10 minutes This measure places the oxygen about the kidney and under the diaphragm When flexion exercises are not feasible manual massage over the kidney may be employed with similar results X ray films are then taken in the antero-posterior and the oblique positions The plate taken in the oblique position has usually given the better visualization Roentgenograms taken in the lateral position are of the least benefit since the spine interferes in this plane

Urinary Gonadotropins[22]

Collect and store in a cool place a 24 hour sample of urine Start test within at most 6 hours after completion of sample

Note volume and take an aliquot for testing

To determine aliquot use

1/4	of entire sample for anticipated high titers	
1/3 to 1/2	" " "	normal
2/3 to 4/4	" "	low

Acidify measured aliquot with glacial acetic acid to pH4 (test with congo red paper)

Add four volumes of 95% ethyl alcohol for each volume of urine

Stir thoroughly cover and place in refrigerator until the precipitate formed settles completely to the bottom of the beaker

Siphon off the supernatant fluid and transfer precipitate quantitatively to 250 ml centrifuge bottles

Centrifuge for about 10 to 15 minutes until precipitate is tightly packed

Decant supernatant fluid

Wash precipitate with 95% alcohol and transfer all of precipitate to one centrifuge bottle

Centrifuge until precipitate is packed and pour off alcohol wash

Wash precipitate with ether centrifuge and decant

Dry precipitate with vacuum or a stream of air This precipitate is stable at room temperature

Assay

With a heavy stirring rod grind dry precipitate to a fine powder and add 15 ml distilled water for normal or high level and 10 ml distilled water for lower levels

Mix well stopper and place in refrigerator over night

Centrifuge and transfer supernatant fluid containing the gonadotropins to a small vial A small precipitate may be insoluble in the water but since it contains no gonadotropins it should be discarded This extract should be stored in the *refrigerator*

Immature female mice weighing between 6 and 10 grams are used for the assay Each mouse receives 5 injections subcutaneously over a period of 3 days 2 on each of the first 2 days (at 9 a m and 5 p m) and 1 on the third The mice are then killed with chloroform 72 hours after the first injection The uterus is removed stripped of attached connective tissue pressed between layers of filter paper to remove fluid and weighed immediately on an analytical or fine torsion balance

Salt Tolerance Test [8]

Procedure

Patients are permitted no fluid after 7 P.M. of the night previous to the test

At 6 A.M. of the morning of the test the patient voids and the urine is discarded. The patient is then given 500 ml of water to drink at one time

All urine from 6 A.M. to 9 A.M. is then collected as one sample (Call this sample A)

At 9 A.M., 200 ml of 5% saline is injected intravenously and all urines from 9 A.M. to 12 M is collected as a second sample (Call this sample B)

Two days later the procedure is repeated with the addition that on the evening previous to the test the patient is injected intramuscularly with 10 mg of desoxycorticosterone acetate

The volume of each urine sample is carefully noted, and both sodium and chlorides are determined in terms of milliequivalents per volume

Subtract the total sodium and chloride ions of sample A from sample B and divide this figure by 171 (meq in 10 grams of salt injected) for the per cent of excreted ions *e g*

Sample A (6–9)	
meq Na/vol	meq Cl/vol
13 1	14 8
Sample B (9–12)	
meq Na/vol	meq Cl/vol
21 8	25 4
171)8 7 = 5 1%	171)10 6 = 6 2%

Calculate samples A and B of the second day s experiment in the same manner

For interpretation of the results compare the percentages of the first experiment with those of the second

Normal individuals show a considerable increase in the percentage of salt retained after the injection of desoxycorticosterone acetate while patients with Cushing s syndrome show a sodium chloride diuresis

Perirenal Insufflation [9 30 31]

Method

The patient is placed on the side in the typical position for exposure of the kidney with 2 or 3 small sandbags under the loin so as to increase the space between the twelfth rib and the iliac crest The patient is rotated somewhat forward so as to allow the peritoneal contents to fall away as much as possible from the site of injection The twelfth rib and the outer edge of the erector spinal muscles are outlined with tincture of mercurochrome An acute angle is thus formed by the junction of these two lines *The skin is then prepared with tincture of iodine as for* any operative procedure The mercurochrome lines will stand out prominently under the iodine coating A small amount of procaine hydrochloride is injected at the 'angle' An ordinary spinal tap needle is introduced in a direction pointing slightly upward toward the twelfth rib and somewhat forward and away from the erector spinal muscles The needle is introduced until Gerota s fascia has been pierced A definite sensation of perforation of this membrane is usually experienced Aspiration at this level is made so as to be sure that the needle does not lie in a vessel The needle is then attached to the oxygen delivery system which consists of a two bottle calibrated pneumothorax outfit and two glass attachments for washing and filtering the oxygen Oxygen is delivered doubly filtered through cotton and washed by 1 to 500 mercury bichloride solution under 6 to 8 inches of gravity

Add 2 ml concentrated hydrochloric acid

Boil on hot plate for 7 to 10 minutes and cool in ice bath

Transfer to a small separatory funnel and saturate with sodium chloride

Shake three times with 25, 15 and 10 ml portions of benzene (If an interface gel should form combine it with the benzene fractions)

The combined benzene extracts are washed

Once with a 15 ml portion of distilled water
Twice " " sodium carbonate
Once " " distilled water

To extract estrogens shake benzene fraction with 4 lots of 2N sodium hydroxide using 20, 15, 10 and 10 ml respectively

Combine sodium hydroxide extracts and acidify by adding 15 ml concentrated hydrochloric acid

Extract three times with benzene using one 20 ml portion and two 15 ml portions

Combine the benzene fractions and wash with

One 15 ml portion of distilled water
sodium carbonate
distilled water

When the benzene fraction has been freed of water evaporate it to dryness and dissolve the dry residue in 1 0 ml 95% ethyl alcohol

Recovery experiments of 0 2 and 0 5 micrograms of estrone as well as a reagent blank of water are run simultaneously

Recovery of estrogen ranges between 50 and 60%

Fluorimetric Assay

Unknown	*Standard*	*Blank*
0 7 ml alcoholic extract	0 2 micrograms estrone	0 7 ml 95% alcohol
8 0 ml sulfuric acid (60–70%)	8 0 ml sulfuric acid (60–70%)	8 0 ml sulfuric acid (60–70%)

Stir thoroughly and place in boiling water bath for five minutes

Cool and read in Coleman photofluorometer Model #12 using a filter combination of B_2 and PC9A

Change to a filter combination of B_1 and PC9A and make a second set of readings

Calculation

$$\frac{\text{Reading of Unknown } B_2\text{-}B_1}{\text{Reading of Standard } B_2\text{-}B_1} \times \text{Conc of standard} \times \frac{1}{0.7} \times \frac{\text{24 hour volume}}{\text{aliquot used}} =$$

Micrograms of estrogens per 24 hours

Normal Values

In normal women during the child bearing period the urinary excretion of estrogens varies daily reaching peak excretions at the mid menstrual interval and again just before the onset of the menses The total 24 hour urinary excretion varies between 15 and 50 micrograms Menopausal women excrete about the same amounts as do normal women between peaks of excretion The daily 24 hour urine value for menopausal women will generally vary from 6 to 7 micrograms although some excrete as much as 20 to 30 micrograms and others less than 5 The daily urinary excretion in adult males is 20 to 26 micrograms while children of both sexes excrete but small amounts rarely in excess of 6 micrograms

In order to make a rough titration of the urinary extract it is wise to divide the mice into 3 groups one group of 3 mice receiving a total of 2.0 cc of extract (i.e. 5 injections of 0.4 ml per injection), another to receive a total of 1.5 ml and a third to receive a total of 0.5 ml.

Untreated controls are run simultaneously with each test case.

If the uteri of at least 2 mice of the 3 in a group weigh 10 mg or over, the test is considered positive at that level.

Calculation

$$\frac{\text{Total vol of urinary extract}}{\text{Total vol of urinary extract injected}} \times \frac{\text{24 hour urine vol}}{\text{Aliquot of urine used}} = \frac{\text{Mouse uterine}}{\text{units/24 hrs}}$$

Normal Values 6–50 mouse uterine units per 24 hours.

If the urinary extract should prove to be toxic to the mice, dialysis is employed in order to remove the offending substances which are usually electrolytes. The same procedure is also employed for the detection of very low titers.

Procedure

Take ½ the volume of a 24 hour sample adding one gram of NaCl for each 100 ml of urine before precipitating with alcohol. Follow the same procedure as above. After the precipitate has been washed and dried, extract 3 times with 10 to 15 ml of distilled water allowing each extraction solution to stand for 30 minutes.

Centrifuge after each extraction and pool all of the solutions.

Transfer the extracts to a cellophane bag and dialyze against running cold water for 4 hours or overnight in 3 liters of distilled water.

Precipitate the dialyzed material by adding

0.1 gram of NaCl

6 volumes of 95% alcohol

Let stand in refrigerator overnight

Siphon off supernatant fluid and transfer precipitate quantitatively to a centrifuge bottle, centrifuge and decant.

Wash precipitate with ether.

Centrifuge, decant and dry precipitate under vacuum.

Assay

This is performed as outlined above. One day before assay is to be started dissolve precipitate in 10 or 15 ml of water. For the detection of subnormal level dissolve in 7.5 ml of water and inject 0.5 ml with each dose. Calculations are then made as indicated above.

Urinary Estrogens[33]

Reagents

1. Hydrochloric acid concentrated
2. Sodium chloride
3. Benzene (A.R. thiophene free) redistilled in an all glass still
4. Sodium carbonate 9%
5. Sodium hydroxide 2 N
   80 grams sodium hydroxide diluted to 1000 ml
6. Ethyl alcohol, 95%
7. Sulfuric acid 60–70%

Procedure

Collect a 24 hour sample of urine.

Take a 20 ml aliquot.

Add 2 ml. concentrated hydrochloric acid.
Boil on hot plate for 7 to 10 minutes and cool in ice bath.
Transfer to a small separatory funnel and saturate with sodium chloride.
Shake three times with 25, 15 and 10 ml. portions of benzene. (If an interface gel should form, combine it with the benzene fractions.)

The combined benzene extracts are washed:

Once with a 15 ml. portion of distilled water
Twice " " " sodium carbonate
Once " " " " distilled water

To extract estrogen. Shake benzene fraction with 4 lots of 2N sodium hydroxide using 20, 15, 10 and 10 ml. respectively.
Combine sodium hydroxide extracts and acidify by adding 15 ml. concentrated hydrochloric acid.
Extract three times with benzene, using one 20 ml. portion and two 15 ml. portions.

Combine the benzene fractions and wash with:

One 15 ml. portion of distilled water
" sodium carbonate
" distilled water

When the benzene fraction has been freed of water, evaporate it to dryness and dissolve the dry residue in 1.0 ml. 95% ethyl alcohol.
Recovery experiments of 0.2 and 0.5 micrograms of estrone, as well as a reagent blank of water, are run simultaneously.
Recovery of estrogen ranges between 50 and 60%.

Fluorimetric Assay

Unknown	*Standard*	*Blank*
0.7 ml. alcoholic extract	0.2 micrograms estrone	0.7 ml. 95% alcohol
8.0 ml. sulfuric acid (60–70%)	8.0 ml. sulfuric acid (60–70%)	8.0 ml. sulfuric acid (60–70%)

Stir thoroughly and place in boiling water bath for five minutes.
Cool and read in Coleman photofluorometer Model #12 using a filter combination of B_1 and PC9A.
Change to a filter combination of B_2 and PC9A and make a second set of readings.

Calculation

$$\frac{\text{Reading of Unknown } B_2\text{-}B_1}{\text{Reading of Standard } B_2\text{-}B_1} \times \text{Conc. of standard} \times \frac{1}{0.7} \times \frac{\text{24 hour volume}}{\text{aliquot used}} =$$

Micrograms of estrogens per 24 hours

Normal Values

In normal women during the child bearing period the urinary excretion of estrogens varies daily, reaching peak excretions at the mid menstrual interval and again just before the onset of the menses. The total 24 hour urinary excretion varies between 15 and 50 micrograms. Menopausal women excrete about the same amounts as do normal women between peaks of excretion. The daily 24 hour urine value for menopausal women will generally vary from 6 to 7 micrograms although some excrete as much as 20 to 30 micrograms and others less than 5. The daily urinary excretion in adult males is 20 to 26 micrograms, while children of both sexes excrete but small amounts rarely in excess of 6 micrograms.

Urinary Estrogens[34]

Reagents

1. Ether, peroxide free
2. Sodium bicarbonate 9%
3. Sodium carbonate 9%
4. Hydrochloric acid, concentrated
5. Sulfuric acid
   Dilute 4 volumes sulfuric acid with 5 volumes of distilled water
6. Sodium hydroxide 0.1 N
   4 grams sodium hydroxide diluted to 1000 ml
7. Ethyl alcohol, redistilled
8. Benzene, thiophene free
9. Phosphoric acid, c.p.
10. Sodium chloride, c.p.

Procedure

Collect a 24 hour sample of urine
Take a 10 ml aliquot
Add 0.7 ml hydrochloric acid (concentrated)
Reflux for 1 hour in an all glass apparatus
Cool under tap water and add 5.6 grams of sodium chloride
Transfer to a separatory funnel and extract 5 times with 20 ml lots of benzene
Pool benzene extracts and wash with 3 ml sodium bicarbonate 9%
Concentrate benzene to 30 ml and wash 3 times with sodium carbonate (9%) using one 30 ml lot and two 15 ml lots
Wash once with 7 ml distilled water
Pool the aqueous and sodium carbonate washes
This fraction contains estriol and is treated separately

Estriol fraction

Acidify the pooled carbonate washes to a pH of less than 6.0 with concentrated hydrochloric acid
Extract 3 times with 35 ml lots of ether
Pool ether extracts and wash
  Twice with 10 ml lots of sodium bicarbonate
  " " distilled water
Evaporate ether to dryness and dissolve residue in a measured volume of ethyl alcohol
If the residue is colored employ the following method of purification
  Dissolve residue in 0.5 ml ethyl alcohol
  Add 50 ml benzene
  Wash with 2 ml sodium bicarbonate
  Extract 3 times with 25 ml portions of 0.01 N sodium hydroxide and once with a 10 ml portion of distilled water
  Pool extracts, acidify with concentrated hydrochloric acid and extract three times with half the volume of ether
  Evaporate ether to dryness and dissolve residue in measured volume of ethyl alcohol

Estradiol Estrone fraction

Wash concentrated benzene extract
  Once with one-fourth its volume of dilute sulfuric acid
  Twice with 15 ml distilled water
Extract 4 times with an equal volume of 1 N sodium hydroxide

Acidify the sodium hydroxide extracts to a pH of less than 5 with concentrated hydrochloric acid and extract 3 times with 50 ml portions of ether

Combine ether extracts and concentrate to 50 ml

Wash the ether

Once with 10 ml portion dilute sulfuric acid

Twice " 20 " sodium carbonate

" " " distilled water

Evaporate ether to dryness and dissolve residue in measured volume of ethyl alcohol

Fluorimetric Assay

Place aliquots of alcoholic extracts in Pyrex test tubes having ground glass stoppers

Evaporate to dryness in an electric oven at 120 C

Cool Add 7 ml *phosphoric acid*

Stopper and heat in boiling water bath in the dark for 30 minute

Cool and measure fluorescence in the Coleman fluorometer using filters B_2 and IC_1

To measure fluorescence of blanks read with filters B_1 and IC_1

Calculation

$$\frac{B_2\text{-}B_1 \text{ of unknown}}{B_2\text{-}B_1 \text{ of standard}} \times \text{Conc of standard} \times \frac{\text{24 hour vol}}{\text{aliquot used}} = \begin{array}{c}\text{Micrograms of estrogen}\\ \text{per 24 hours}\end{array}$$

Urinary Pregnanediol[15]

Reagents

1 Toluene sulfur free
   Distil twice in an all glass still
2 *Hydrochloric acid concentrated*
3 Sodium hydroxide 1 normal
   Dissolve 40 grams sodium hydroxide in 1000 ml distilled water
4 Ethyl alcohol
   Reflux over sodium hydroxide and distil twice in an all glass still
5 Hyflo-Super Cel
   Johns Manville Co
6 Alcohol water mixture
   Mix 1 volume of alcohol with 4 volumes of distilled water
7 Norite
8 Sulfuric acid concentrated

Procedure

Collect a 24 hour urine sample using 5 ml of toluene as a preservative

Make up to 2500 ml and remove two aliquots of 500 ml each

Place in a 1000 ml flask

Add 100 ml toluene and bring to a boil under a reflux condenser

To the boiling mixture add 50 ml concentrated hydrochloric acid and continue boiling for exactly 10 minutes

Cool flask rapidly and transfer contents to a separatory funnel

Shake Let stand and draw off the urine

Filter the toluene layer and the *emulsion formed with gentle suction through* a Whatman #1 filter paper on a Buchner funnel

Extract twice again with 100 ml toluene filtering each time

Combine toluene fractions and transfer to a clean separatory funnel

Wash

Twice with 100 ml portions of normal sodium hydroxide
" " " " distilled water

Transfer toluene to a round bottom flask and evaporate nearly to dryness on a hot plate

Place in a water bath and take to complete dryness under vacuum

Transfer dry residue quantitatively with warm ethanol to a 20 ml conical centrifuge tube and evaporate to dryness in a water bath under a stream of air

To dry residue add exactly 4 0 ml ethanol and place in a beaker of water at 75

Completely dissolve residue by stirring with a glass rod and add drop-wise from a burette 16 0 ml of 0 1N sodium hydroxide (The addition of the sodium hydroxide should take about 3 minutes)

Allow the tube to remain at 75 C temperature for an additional minute and then transfer beaker and tube to incubator at 37 C

Let stand overnight

Add approximately 8 to 10 mg Hyflo-Super Cel and mix with a stirring rod Wash rod with ethanol water mixture and centrifuge for 1 hour at 1500 r p m

Remove supernatant fluid by suction

Repeat precipitation 2 times more using water instead of sodium hydroxide and incubating for 2 hours instead of 24

To final precipitate add 5 ml of ethanol and dissolve by stirring and warming to 75 C

Add 1 to 2 mg Norite and continue warming for 2 minutes

Filter into a test tube through a small Whatman #1 filter paper washing tube and filter 3 times with 2 ml portions of warm ethanol

Evaporate filtrate and washings in a water bath under a stream of air and take to complete dryness in a vacuum desiccator over calcium chloride

Colorimetric Assay

To dry pregnanediol add 10 0 ml sulfuric acid (concentrated)

Place in water bath at 25 C for 20 minutes shaking occasionally

Measure intensity of yellow color produced in a photoelectric colorimeter using a filter with an absorption maximum of 420 mu

Refer to a calibration curve made with known amounts of pure pregnane-3(α) 20 α-diol varying from 0 1 to 0 5 mg

Make a fresh calibration curve each time

(If on inspection of the dry residue of the unknown sample there should appear to be more than 5 0 mg dissolve it in a measured volume of ethanol and use an aliquot for the colorimetric assay)

Oral Glucose Tolerance Test[16]

Determine the patient s weight

Prepare a weighed amount of glucose equivalent to 1 75 grams of glucose for every kilogram of the patient s weight

Dissolve the glucose in the ratio of 4 grams per 10 ml of water adding the juice of 1 lemon for flavor

The patient is fasted from 7 P M of the night before the test until the test is completed

Obtain a fasting blood sugar and a specimen of urine at the same time

Exactly ½ hour after the sugar drink has been taken another blood sugar and specimen of urine are collected

Repeat this procedure at the end of 1 2 and 3 hours

In a normal result the highest level is not more than 30 to 60 mg above the fasting level and the fasting level is reached in 2 hours There is no glycosuria Normal fasting levels are between 90 and 120 mg % In diabetes the level attained is higher and there is a failure of return to the normal level by the end of the second to third hour There may be glycosuria In renal glycosuria the curve is normal but sugar appears in the urine Increased sugar tolerance (a flat curve or only a slight rise less than 30 mg) occurs in hypophyseal dysfunction Addison s disease hypothyroidism and muscular dystrophy Disease of the small intestine may result in a flat curve because of poor absorption (celiac sprue)

Intravenous Glucose Tolerance Test[37]

The test is performed on a fasting subject and a control sample of blood is obtained for sugar analysis

50 ml of a 50% solution of glucose in distilled water is injected over a 2 minute period

Samples of blood are obtained at half hourly intervals for a period of 2 hours

If a blood sugar level at the end of 2 hours exceeds 120 mg % the patient probably has diabetes while a blood sugar of less than 100 mg % excludes diabetes

Results between 100 and 120 mg % are indeterminate

Exton Rose Glucose Tolerance Test[38]

This glucose tolerance test is carried out after the patient has fasted overnight However he should have taken at least 100 grams of carbohydrate daily for 3 days prior to the test

Technic

1 Dissolve 100 grams of glucose in 650 ml of water flavored with lemon juice
2 Collect a control blood and urine
3 Have patient drink one half the total dose of glucose water within a minute
4 30 minutes after the ingestion of this portion collect blood and urine
5 Directly after collection of blood give the remaining portion of glucose water
6 30 minutes after ingestion of second dose collect blood and urine

Results

In normal patients a rise not exceeding 75 mg of sugar over the control level is present in the 30 minute specimen The blood sugar level of the hour sample should not exceed the 30 minute specimen by more than 5 mg Normally the blood sugar at the end of 1 hour is less than that at the end of 30 minutes All urine specimens should be *free of sugar* as tested with Benedict s qualitative reagent

In diabetes there is a rise of not less than 10 mg per cent of the blood sugar in the 60 minute sample following the second dose of glucose and the blood sugar value usually exceeds 160 mg per cent

The Insulin Tolerance Test (Hypoglycemia Responsiveness)[39]

The test is performed after a 12 hour fast and either capillary or venous blood for sugar determinations may be used The standard test consists of the intravenous injection of 0 1 unit per kilogram of body weight of regular insulin Where severe hypopituitarism or Addison s disease is suspected the insulin dosage should be reduced to one third the standard dose (0 033 units per kg of body weight) If the latter fails to produce a fall in the blood sugar to approximately 45 per cent of the fasting level the test should be repeated with the standard insulin dosage

A control sample of blood is obtained and again 20, 30, 45, 60, 90 and 120 minutes after the insulin injection for blood sugar determination. The insulin tolerance test is inapplicable when the fasting blood sugar level is above the normal range. The test is also not indicated when the fasting blood sugar is below the normal range and within hypoglycemic levels since this in itself would indicate hypoglycemic unresponsiveness.

The maximum fall in the blood sugar level occurs within the first 20 to 30 minutes in normal individuals and in patients with *Addison's disease*, *hypopituitarism* and anorexia nervosa. In primary myxedema the reduction is definitely slower and the blood sugar reaches the lowest level in approximately *45 minutes*. The return of the blood sugar to control levels occurs within 2 hours in normal individuals and in most patients with anorexia nervosa. In *hypopituitarism*, *Addison's disease* and in some patients with anorexia nervosa, the hypoglycemia unresponsiveness is characterized by an abnormally slow return of the blood sugar to the control level. In primary myxedema there is a similar delay but this is perhaps the result of the late development of the hypoglycemia rather than an evidence of a delayed response to the hypoglycemia.

The fall in the blood sugar level following the injection of insulin is usually associated with some clinical hypoglycemic manifestations such as a sense of anxiety, hunger, dizziness, tachycardia and sweating. Clouding of consciousness evidenced by confusion in understanding or answering questions, and coma call for prompt interruption of the test by the administration of adrenalin intramuscularly or glucose intravenously, or the oral use of sweetened drinks.

Glucose Insulin Tolerance Test[39]

In this test the amount of glucose given is that given in the glucose tolerance test. The amount of insulin is that given in the insulin tolerance test.

Both the glucose and insulin are administered simultaneously and blood samples are collected at 0, 20, 30, 45, 60, 90 and 120 minutes.

Hexosamine in Serum[40]

Reagents

1. Physiologic saline
   9.0 grams sodium chloride dissolved in distilled water and diluted to 1000 ml.
2. Hydrochloric acid, 2 normal
   164 ml. concentrated hydrochloric acid diluted to 1000 ml. with distilled water.
3. Sodium hydroxide, 0.5 normal
   20 grams sodium hydroxide dissolved in distilled water and diluted to 1000 ml.
4. Acetyl acetone reagent
   Redistil acetyl acetone in an all glass still.
   Dissolve 1 ml. acetyl acetone in 50 ml. 0.5 normal sodium carbonate.
   Stored in the refrigerator this solution will be stable for 3 to 4 days.
5. Ethyl alcohol, 95%
   Redistil in an all glass still.
6. Ehrlich's reagent
   Dissolve 800 mg. p-dimethylaminobenzaldehyde in 30 ml. of 95% ethyl alcohol and add 30 ml. of concentrated hydrochloric acid. Stored in the refrigerator this solution will be stable for 10 days.
   To purify p-dimethylaminobenzaldehyde:
   Dissolve 125 grams of the aldehyde in 700 ml. of dilute hydrochloric acid (1 part concentrated HCl sp. gr. 1.19 to 6 parts distilled water).
   Place in beaker and dilute with half the volume of distilled water.

Add dilute sodium hydroxide (15 to 20%) slowly with mechanical stirring
Filter off the first precipitate and discard This will be lightly colored
Precipitate the rest of the aldehyde by the further addition of sodium hydroxide
Filter and dry
Collect only the white precipitate

7 Stock standard
Dissolve 100 mg glucosamine hydrochloride in distilled water and dilute to 100 ml
Store in refrigerator and prepare fresh every 3 weeks
Dilute daily for working standard

Procedure

Dilute 1 ml serum to 10 ml with physiologic saline
Transfer 2 ml diluted serum to a 10 ml volumetric flask
Add 2 ml 2 normal hydrochloric acid
Stopper and place in boiling water bath for 5 hours
Remove from boiling water and cool under tap water
Dilute to 10 ml mark and filter through a Whatman #5 filter paper

Trial titration for neutralization

A 1.0 ml aliquot of the filtrate is titrated carefully with 0.5 normal sodium hydroxide to determine the amount necessary to neutralize the sample For the colorimetric assay this quantity of sodium hydroxide is added to each filtrate

Colorimetric Assay

Into a 10 ml volumetric flask place
1.0 ml filtrate
0.5 normal sodium hydroxide (quantity determined as above)
1.0 acetyl acetone reagent
Mix stopper and place in boiling water bath for 25 minutes
Remove and cool in water bath for 2 minute

Add
3.0 ml 95% ethyl alcohol
1.0 ml Ehrlich s reagent
Shake gently and place in hot water for 3 minutes
Remove and place in cold water for 3 minutes
Dilute to 10 ml with alcohol stopper and mix well
Let stand for 30 minutes and read in photoelectric colorimeter using a green filter with a maximal absorption at 525 mu
Standard solutions containing 0.02 0.04 and 0.06 mg of glucosamine as well as a blank of all reagents are run simultaneously

Calculation

$$\frac{\text{Reading of unknown}}{\text{Reading of standard}} \times \text{mg of standard} \times \frac{100}{0.02} = \text{mg glucosamine/100 ml serum}$$

Normal Values 90 to 120 mg/100 ml

The Male Frog Test for Early Pregnancy[11]

Male frogs Rana pipiens are used for the test The first morning sample of urine is collected and 5 ml injected subcutaneously into the dorsal or lateral lymph

sacs of the frog Each frog is placed in a separate clean dry glass jar with a perforated lid and is set aside at room temperature for 2 to 4 hours At the end of this time any urine excreted is examined microscopically for spermatozoa If none are present the urine is drained from the jar care being taken to leave the frog undisturbed The frog is then seized in the hand while still in the jar This pressure usually induces another urination and this specimen is then examined for spermatozoa

When spermatozoa are present the test is positive

The test animals may be used for another test after 4 or 5 days

Aschheim Zondek Test for Pregnancy[4]

Immature mice 3 to 4 weeks old weighing 6 to 8 grams are used for the assay The first morning specimen of urine is collected and from 1 2 to 2 4 ml are injected subcutaneously in 6 equal injections over a period of 48 hours Ninety six hours after the first injection the mice are sacrificed and the ovaries examined for corpora hemorrhagica

The test is considered positive if there is a single hemorrhagic follicle or corpus luteum

Friedman Test for Pregnancy[13]

Two adult female rabbits weighing not less than 800 grams are used They are kept isolated from the male for at least 4 weeks prior to the test The first morning sample of urine is collected and on each of two successive days 10 ml are injected into the marginal vein of the ear Forty eight hours after the first injection the rabbits are killed or simply anesthetized and the ovaries examined

The presence of enlarged hemorrhagic follicles constitutes a positive test

The rabbits may be used several times provided an interval of 1 month is allowed between tests

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